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Formulation and *In-Vitro* Evaluation of Tadalafil Fast Disintegrating Tablets With Poloxamer

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ABSTRACT

In the present work Tadalafil fast disintegrating tablets were prepared with poloxamer as carrier to enhance the solubility of Tadalafil and in order to disperse at faster rate in the mouth. Chemically Tadalafil is (6R,12aR)-6-(1,3-Benzodioxol-yl) 2,3,6,7,12,12a hexahydro-2-methylpyrazino[10,20:1,6] pyrido [3,4-b]indole-1,4-dione used in erectile dysfunction. In this current work Tadalafil fast disintegrating tablets were formulated from F1-F12 by direct compression method by taking 1:1, 1:2 and 1:3 ratio of poloxamer as a water soluble polymer and super disintegrating agents such as crospovidine, croscarmellose sodium, sodium starch glycolate and kryon. There after FT-IR studies were performed and it was observed that there were no incompatible reactions found between the Tadalafil and excipients used in formulations. Then all the formulations of Tadalafil fast disintegrating tablets F1-F12 were evaluated for pre and post compressional parameters including in-vitro dissolution studies. In which formulation F-12, containing (1:3) ratio of drug-poloxamer and kryon as super disintegrating agent was shown significant changes in wetting time (13±2.09sec), dispersion time (36±3.605sec) and fastest percentage drug release of 99.27±2.78 within 30 minutes was observed.

Keywords: Tadalafil, Poloxamer 407, Crospovidone, Croscarmellose sodium, Sodium starch gycolate, Kryon T314 etc.

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INTRODUCTION

Among the different routes of administration, the oral route of administration continues to be most preferred route due to various advantages including ease of administration, avoidance of pain, versatility and most importantly patient compliance. Tablets are the most widely used dosage forms because of its convenience in terms of self-administration, compactness and ease in manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of pediatric and geriatric patients. Recent advances in novel drug delivery (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for ease of administration and to achieve better patient compliance. One such approach is oral disintegrating tablets (ODTs).[1, 2, 3]

United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute. ODT's are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets and rapidmelts.[4,5] In the present work Tadalafil (figure:01) was used as drug which appear in white crystalline powder with molecular weight of 389.40 g/mol having very good specific Type V phosphodiesterase inhibitor activity. Through the inhibition on PDE-V, lead to increased concentrations of cGMP, producing smooth muscle relaxation and increased blood flow to the corpus cavern sum, thereby enhancing erectile response following appropriate sexual stimulation, but it was very poorly insoluble drug and shows poor absorption. By taking the account of poor solubility of Tadalafil, work was planned to formulate and evaluate fast disintegrating tablets in order to ensure increased bioavailability, due to rapid disintegration and dissolution of Tadalafil fast disintegrating tablets.[6, 7]

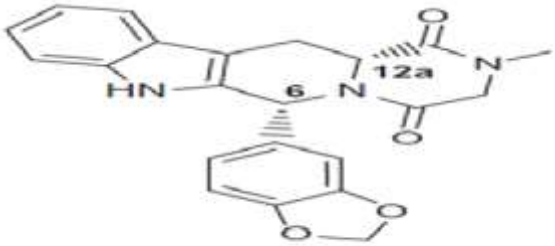

Figure: 1 Chemical formula of Tadalafil

MATERIALS AND METHOD

Tadalafil obtained from Hetero Drugs Pvt Ltd, Hyderabad as a gift sample, Poloxamer 407 obtained from DR.Reddy's Laboratories Hyderabad, Crospovidone, Croscarmellose sodium, Sodium starch gycolate, Kryon T314 were gift samples from Aurobindo Pharmaceuticals Hyderabad, Microcrystalline cellulose, Mannitol (SD Fine Chemicals Pvt Ltd, Mumbai), Magnesium stearate and Talc (Qualikems Fine Chem Pvt Ltd, Vadodara). All the above following materials were either AR/LR grade have used in the above work.

Formulation of Tadalafil fast dissolving tablets

Preparation of Tadalafil solid dispersions

Solid dispersions (SDs) of Tadalafil were prepared by using poloxamer as a carrier, (drug: polymer ratio was taken 1:1, 1:2 and 1:3) by melting method. Firstly Poloxamer was melted at 60°C then Tadalafil was added to the molten polymer, mixed well and allowed to cool at room temperature to get a solidified mass which was crushed and passed through sieve 100.

Formulation design

Take the required quantity of powdered and crushed Solid dispersions (SDs) of Tadalafil and blended with selective super disintegrating agent, microcrystalline cellulose as a filler, Mannitol, Menthol, Magnesium stearate as lubricant and Talc as a glidant by geometric dilution,. Then all the ingredients were passed through sieve no. 80 and the tablets were punched by using 8mm die with flat surface on rotary tablet compression machine (Cadmach).

Table: 1 Formulation of Tadalafil Fast disintegrating tablets from F1-F12

Ingredients	**F1 (1:1)**	**F2 (1:2)**	**F3 (1:3)**	**F4 (1:1)**	**F5 (1:2)**	**F6 (1:3)**	**F7 (1:1)**	**F8 (1:2)**	**F9 (1:3)**	**F10 (1:1)**	**F11 (1:2)**	**F12 (1:3)**
Tadalafil-Poloxamer(SDs)	40	60	80	40	60	80	40	60	80	40	60	80
Crospovidone	12.5	12.5	12.5	-	-	-	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	12.5	12.5	12.5	-	-	-	-	-	-
SSG	-	-	-	-	-	-	12.5	12.5	12.5	-	-	-
Kryon	-	-	-	-	-	-	-	-	-	12.5	12.5	12.5
MCC	50	50	50	50	50	50	50	50	50	50	50	50
Mannitol	137.5	117.5	97.5	137.5	117.5	97.5	137.5	117.5	97.5	137.5	117.5	97.5
Menthol	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	250	250	250	250	250	250	250	250	250	250	250	250

Evaluation of pre-compressional parameters

Preformulation studies were performed on the drug, which included identification of pure drug and physicochemical properties of the bulk drug like physical appearance, solubility, melting point,

drug-excipient interactions by FT-IR, bulk density, tapped density, compressibility index and angle repose etc.

FT-IR studies

The drug and optimized formulation were characterized by FTIR Spectroscopy using a FT-IR 8400S (Shimadzu, Japan). The spectra were taken by KBr with pressed pellet technique in the range of 4000-500cm^{-1}.

Flow properties of powder blend

The angle of repose (θ) of the granules was determined by using funnel method. Bulk density (BD) and tapped density (TD) were calculated by formula: BD = Bulk mass/Bulk volume; TD = Bulk density = Bulk mass/Bulk volume. Compressibility index and Hausner's ratio of the granules was determined by using the formula: CI (%) = [(TD-BD/BD)]×100 and HR = TD/BD, respectively. The experiments were performed in triplicate and average values with SD were noted. [8]

Evaluation of post-compressional parameters

The thickness of the tablet is measured by Digital vernier calipers. 20 tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight. Tablets were evaluated for hardness using Monsanto hardness tester and friability using Roche friabilator. For the estimation of drug content, tablets were randomly selected and powdered finely. The powder equivalent to one tablet was added to 100ml of methanol in a conical flask and placed on a rotary shaker. The solution was filtered through a 0.22µ filter then absorbance was measured using Systronics UV–Vis spectrophotometer, against 0.1 N HCl solutions as blank at a wave length of 284 nm.

For estimation wetting time and water absorption ratio, A tablet was carefully placed on the surface of tissue paper in the petridish at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time.[9]

The Water absorption ratio, R, was determined according to the following equation:

$R = 100 (Wa - W_b) / W_b$; W_b and W_a are the weight before and after water absorption respectively.

Disintegration of tablets was determined using a USP disintegration testing apparatus type II (Paddle) (Electrolab ED-2L, India). In which tablets were placed into an apparatus and disintegration time was recorded. [10]

***In-vitro* dissolution study**

The drug release was determined using USP - II rotating paddle type apparatus (Electrolab TDT-08L, India) at 75 rpm using 900ml of pH 1.2 buffer solutions as dissolution medium and temperature was maintained at 37 ± 0.5 ºC. Aliquot of 5 ml of dissolution medium was withdrawn

at specified time intervals i.e 5, 10, 15, 20, 25 and 30mins and the absorbances of solutions were measured by UV spectrophotometric method at 284 nm and concentration of the drug was determined from standard calibration curve.[11]

Stability study

Stability study was done for the optimized formulation for a period of three months at 40±2^{o}C and 70±5% RH to provide evidence on how the quality of a drug substance varies with time under the influence of a variety of environmental factors such as temperature, humidity, light and enables recommended storage conditions, re-test periods and shelf-lives to be established.[12, 13]

RESULTS AND DISCUSSION

Fast disintegrating tablet are one of the approaches in order to increase the solubility as well as absorption. Attempts have been made for preparation of FDTs with variable ratios of drug-polymer mixture and different concentrations of superdisintegrants such as crospovidine, croscarmellose sodium, sodium starch glycolate and kryon for enhancing the release pattern according to marketed formulation and USP guidelines of Tadalafil fast disintegrating tablets. Figure. 1 & 2 demonstrates the FT-IR spectrum of pure Tadalafil and Optimized formulation (F12).

By practical examination of Tadalafil through FT-IR studies revealed characteristic absorption bands at particular frequency number of 3328, 2904, 1677, 1649,1489, 1438, 1401, 1323, 1269, 1242, 1152, 1097, 1041, 939, 922, 746 cm^{-1}

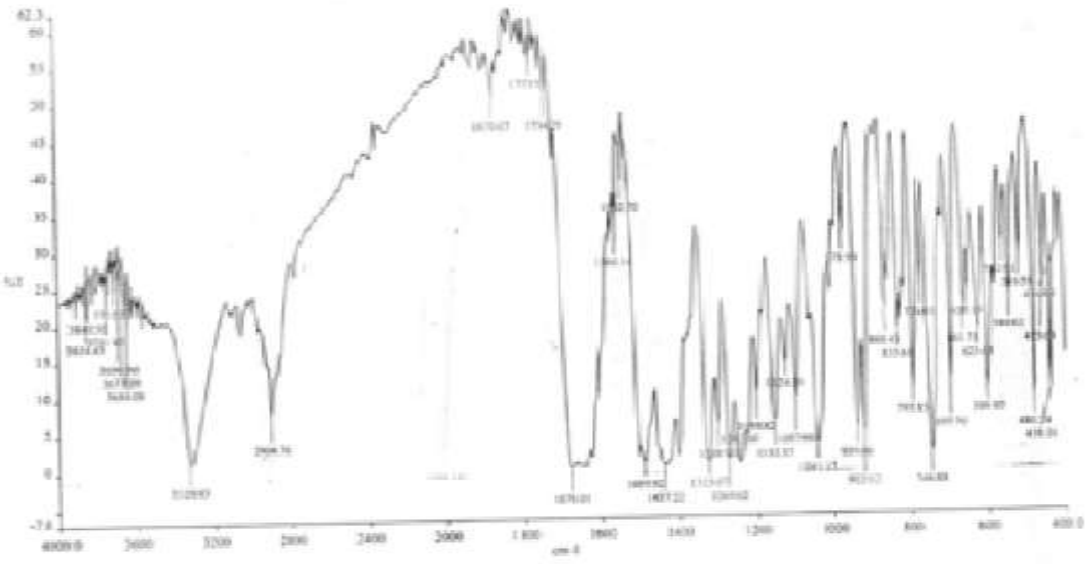

Figure: 1 FT-IR spectrum of pure Tadalafil

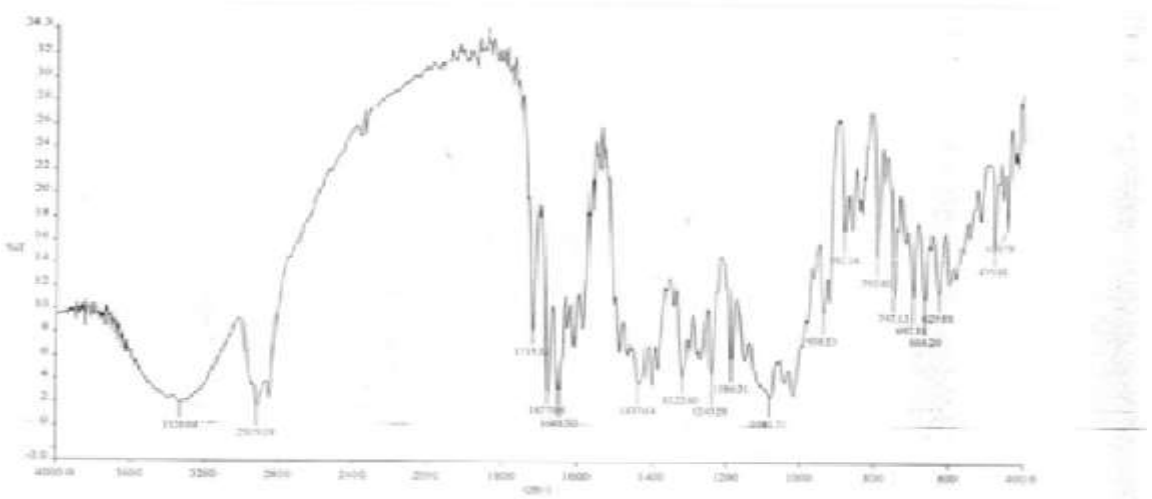

Figure: 2 FT-IR spectrum of optimized formulation of Tadalafil F12

The above similar characteristic peaks were observed both in the pure Tadalafil and optimized formulation (F12). These results indicating that there was no incompatibility between the drug and excipients used.

The FDTs of Tadalafil were evaluated for various physical properties (Table 2). The bulk densities for the powder blend of Tadalafil tablets of various formulations (F1-F12) ranged between 0.341±0.176g/ml and 0.390±0.003 g/ml; and tapped density ranged between 0.303±0.014g/ml and 0.326±0.031g/ml when determined by the tap densitometer. These values of bulk density indicate good packing characteristics. The Carr's index (CI) for all the formulations were ranged from 9.14±0.09 to 14.93±0.93, indicating desirable flow properties. The value of Hausner's ration was ranged from 1.10±0.04 to 1.24±0.09. The flow properties of powder blends were further analyzed by determining the angle of repose for all formulations; values ranged between 21.33±2.08 and 27.67±1.52.

Evaluation of Tadalafil Fast disintegrating Tablets

All the formulations (F1-F12) were produced under similar conditions to avoid processing variables. The weight variation, hardness, friability, thickness and content uniformity of all formulations were found to be within acceptable limits as per official specifications. Weight of the optimized Tadalafil FDTs formulation (F12) was 250.1±1.24 mg, hardness was 3.24±0.249kg/cm^2 and thickness was 3.03±0.188mm. The percentage friability of all the formulations was ranged from 0.39±0.026 to 0.51±0.025 which were less than 1% of their weight. Values of the hardness test and percent friability indicated good handling properties of the prepared Tadalafil FDTs. The drug content (assay) uniformity in the Tadalafil tablets was ranged from 98.13±0.460 to

99.95±0.836 %. Further Disintegration, wetting time and water absorption ratio of FDTs Tadalafil optimized formulation (F12) was found to be15±1.05sec, 13±2.09sec and 36±3.60 sec respectively.

***In vitro* drug release study**

The results of *in vitro* drug release profile of Tadalafil FDTs shown in figure 3,4. In which the selective combination of drug-polymer ratio and variable concentration of preferred super disintegrating agents play important role in the retardation and optimization of the drug release as well as increases the retardation of drug release tablet. The percentage drug releases of all the formulations (F1-F12) were shown in the range of 70.54±2.56 to 99.27±2.78 respectively.

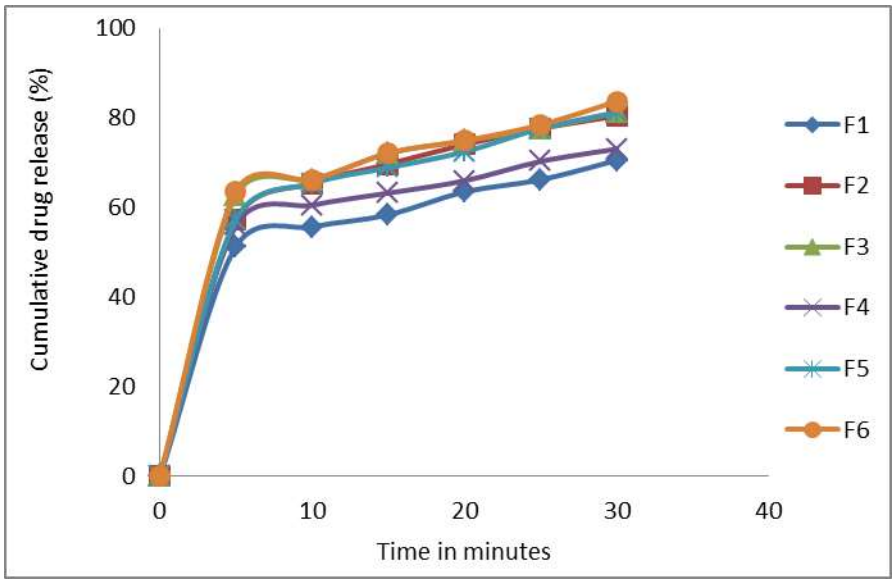

Figure: 3 *In vitro* Dissolution profile of Tadalafil FDTs from F1-F6

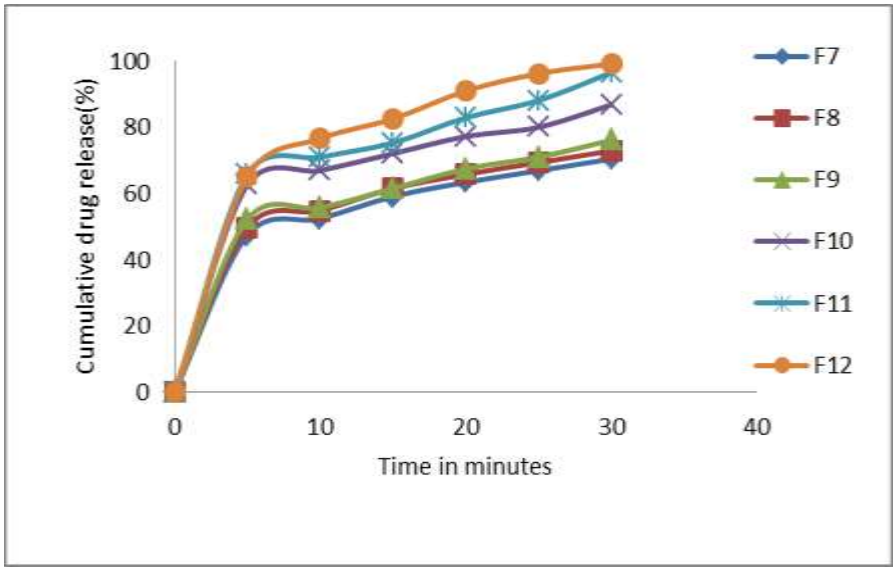

Figure: 4 In vitro Dissolution profiles of Tadalafil FDTs from F7-F12

Comparison Dissolution profile using Similarity Factor, *f*2

Moore and Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors, *f*1 and *f*2.

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

When the two profiles are identical, *f*2=100. An average difference of 10% at all measured time points result in an *f*2 value of 50. FDA has set a public standard of *f2* value between 50-100 to indicate similarity between two dissolution profiles and it was shown in figure: 05

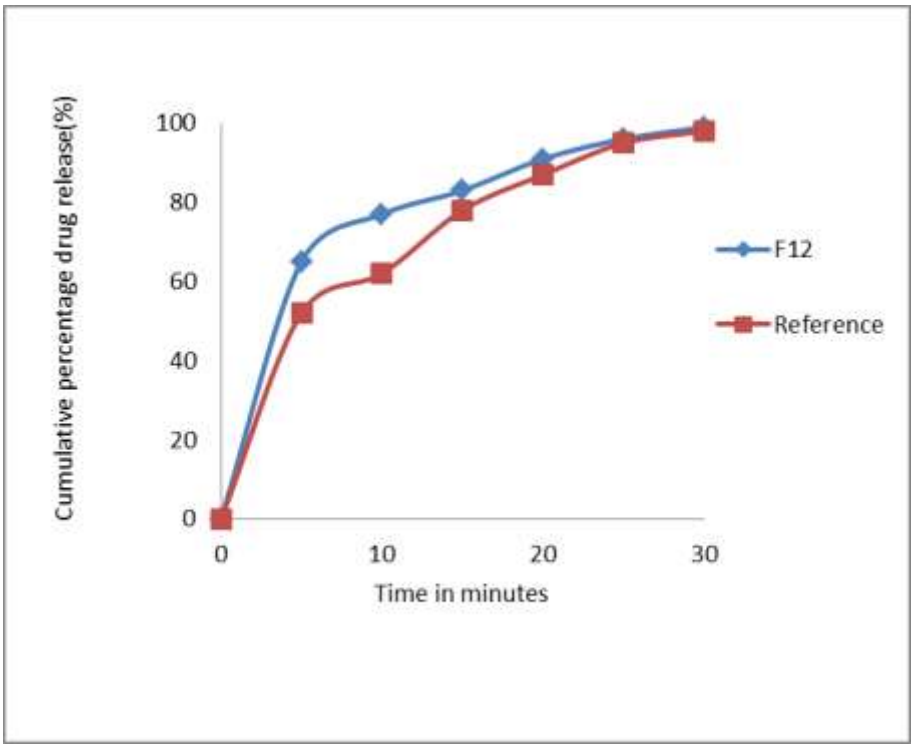

Figure: 5 Comparison of Dissolution profile using Similarity Factor *f*2

Comparing the optimized formulation with marketed product, there appears to be an average difference of 10% at all measured time points in the release rate of the drug from the dosage form. Since the similarity factor shows a value of 53, there appears to be a similarity between F12 and marketed product.

Stability studies

The accelerated stability studies (Table 2) were carried out on the optimized formulation, ie., F12. The formulation was stored at 40±2^{o}C, 75±5% RH for 3 months to assess their long term stability. After stability study, tablets were subjected to various tests like hardness, thickness, friability, drug content and *in vitro* drug release study. The results indicated that there were no changes observed in tablets characteristics after a period of 3months stability study.

Table: 2 Stability studies of optimized formulation (Tadalafil –F12) at 40±2 °C & 75±5%RH

Time period	Description (colour)	Friability (%)	Hardness (kg/cm^2)	Drug content uniformity (%)
Initial	White	0.49±0.015	3.24±0.249	99.95±0.836
I st month	White	0.48 ± 0.06	*3.22 ± 0.03*	99.94 ± 0.01
II nd month	White	0.48 ± 0.02	*3.21± 0.09*	99.92 ±0.07
III rd month	White	0.46 ± 0.01	*3.21 ± 0.05*	99.81 ± 0.02

CONCLUSION

An attempt was made to formulate and evaluate fast disintegrating tablets of tadalafil, which is mainly used for erectile dysfunctioning. FT-IR study was carried out to find out the possible interaction between the Tadalafil with excipients. Then the result revealed that there was no interaction between the selected drug and excipients used. Tadalafil fast disintegrating tablets were prepared by direct compression method and carried out all possible pre and post compressional parameters. From these results, it was found that the physicochemical parameters of the prepared tablets comply with the standards.

Finally the *In vitro* release of Tadalafil from the prepared FDTs was studied using pH 1.2 as a medium, in which formulation F12 containing Tadalafil-poloxamer raito (1:3), Kyron as super disintegrating agent shown fastest drug release 99.27±2.78 within 30 minutes. These results were indicating that the time required for drug to release from tablet was decreased, with increasing the concentration of drug to poloxamer by using crospovidone and croscarmellose sodium and kryon as superdisintegrants. However, time required for drug release was increased with higher concentration of.kryon, because it acts as both superdisintegrant and dissolution enhancer.

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