FORMULATION DEVELOPMENT OF IMMEDIATE RELEASE TABLETS OF TADALAFAIL WITH QUALITY BY DESIGN PERSPECTIVE.

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ABSTRACT:

In present study, immediate release tablets of Tadalafil were prepared with wet granulation process and are evaluated for drug release. The drug release profile was compared with marketed product. Saturation solubility studies were performed for dissolution media selection and was found that Tadalafil has pH independent solubility and also it was found that solubility increases with addition of surfactant. Tablets prepared with wet granulation process showed significant improvement in drug release when compared with marketed product. Factorial design of experiments were conducted to find out significant factors are influencing drug release. Macrogol cetostearyl ether and Hydroxy propyl methyl cellulose were found to significantly increase the release profile in the selected dissolution medium. pXRD results indicate that crystalline form of Tadalafil is retained in the formulation.

INTRODUC

Formulation development of poorly soluble drugs is very challenging. More specifically developing immediate release dosage forms for these poorly soluble drugs is still more difficult[1]. Drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution of the drug substance under physiological conditions, and the permeation across the gastrointestinal membrane. Immediate-release dosage form drug products containing low solubility drug substances are considered to high risk regarding the impact of dissolution on in vivo performance[2]. Dissolution from the dosage form involves release of the drug from the formulation followed by the dissolution of the drug in dissolution medium[4]. The overall rate of dissolution depends on the slower of these two steps. In the first step of dissolution, the properties like disintegration of the formulated drug play a important role. If the first step of dissolution is rate-limiting, then the rate of dissolution is considered disintegration controlled. In the second step of dissolution the physicochemical properties of the drug such as its chemical form and physical form) play an important role[5]. If this latter step is rate-limiting, then the rate of dissolution is dissolution controlled. This is the case for most poorly soluble compounds in immediate-release formulations whose solubility is less than 2 mg/L through out the entire gastro intestinal pH[6]. Taladalfil is a poorly soluble and highly permeable drug with pH independent solubility. It is well known that poorly soluble drugs lead to poor dissolution, which leads to incomplete release from the dosage form[7]. So there is a need to develop immediate release tables of Tadalafil with complete release from the dosage form. Drug release is usually the rate limiting process for absorption of a compound. Tadalafil is an insoluble drug and therefore release of the drug is the rate limiting step[8]. Hence the objective of this study is to develop an immediate release tables of Tadalafil using wet granulation process which shows higher drug release profile when compared to marketed product in selected dissolution medium.

MATERIAL AND METHODS:

Materials

Tadalafil was obtained as gift sample from Glenmark Pharmaceuticals, Limited. Mannitol was obtained as gift sample from Roquette Pharma. Lactose anhydrous was obtained as gift sample from DFE pharma. Sodium starch glycollate was obtained as gift

sample from JRS pharma. Hydroxypropylmethyl cellulose was obtained as gift sample from Ashland Pharma. Magnesium stearate was obtained as gift sample from Roquette Pharma. Macrogol cetostearyl ether was obtained as gift sample from BASF, India and colloidial silicon dioxide was obtained as gift sample from Evonik.

Saturation solubility studies:

Saturation solubility studies were carried out for 24 hours in different aqueous media (Water, 0.1 NHCL, 4.5 Acetate buffer and 6.8 Phosphate buffer)

In vitro drug release studies:

In-vitro dissolution studies of Tadalafil tablets were carried out in 1000 ml of 0.5% Sodium Lauryl Sulfate in water, 50 RPM, Type II as dissolution medium. The temperature was maintained at 37 ± 0.5°C. 5mL aliquots were withdrawn at 5, 10, 20, 30, 45 and 60 minutes and filtered using a 0.45µ nylon filters and replaced with 5mL of fresh dissolution medium. The filtered samples were suitably diluted and analyzed using HPLC UV detector at 285 nm.

Preparation of tablets:

The values of Hauser ratio and Compressibility Index of Tadalafil API indicated poor flow and poor compressibility behavior. Hence direct compression technique was not adopted. The tablets were manufactured with wet granulation technique to avoid flow issues.

Table 1: Formulation compositions with wet granulation technique.

Ingredients	TD1A	TD1B	TD2A	TD2B	TD3A	TD3B
Tadalafil	5.00	5.00	5.00	5.00	5.00	5.00
Lactose anhydrous	150.00	150.00	150.00	150.00	150.00	150.00
Hydroxypropyl methyl cellulose	-	-	5.00	10.00	5.00	10.00
Sodium Starch glycolate	10.00	10.00	10.00	10.00	10.00	10.00
Macrogol cetostearyl ether	5.00	10.00	-	-	5.00	10.00
Water	q.s	q.s	q.s	q.s	q.s	q.s
Extra granular portion						
Mannitol	110.00	105.00	110.00	105.00	105.00	95.00
Sodium Starch glycolate	15.00	15.00	15.00	15.00	15.00	15.00
Colloidal silicon dioxide	2.00	2.00	2.00	2.00	2.00	2.00
Magnesium stearate	3.00	3.00	3.00	3.00	3.00	3.00
Total	300.00	300.00	300.00	300.00	300.00	300.00

Manufacturing process:

For Formulations TD1A, TD1B: Lactose anhydrous and Sodium Starch glycolate were sifted through 40# mesh and added into rapid mixer granulator and dry mixed for 10 minutes at slow speed. Macrogol cetostearyl ether and Tadalafil were added to purified water and stirred to form a uniform dispersion which is used as a granulating liquid.

For Formulations TD2A, TD2B: Lactose anhydrous and Sodium Starch glycolate were sifted through 40# mesh and added into rapid mixer granulator and dry mixed for 10 minutes at slow speed. Hydroxypropylmethyl cellulose ether and Tadalafil were added to purified water and stirred to form a uniform dispersion which is used as a granulating liquid.

For Formulations TD3A, TD3B: Lactose anhydrous and Sodium Starch glycolate were sifted through 40# mesh and added into rapid mixer granulator and dry mixed for 10 minutes at slow speed. Hydroxypropylmethyl cellulose, Macrogol cetostearyl ether and Tadalafil were added to purified water and stirred to form a uniform dispersion which is used as a granulating liquid.

For Formulations TD1A to TD3B

The dry mix of formulations TD1A to TD3B were granulated with respective granulating fluids. The wet granules were dried at 60°C inlet temperature. The dried granules were sifted through 40# mesh. Mannitol, Sodium Starch glycolate and Colloidal silicon dioxide were sifted through 40# mesh and add to sifted dried granules and blended for 10 min. Magnesium Stearate sifted through 60 mesh was added into prelubricated blend and continued blending for 5 min and then compressed into tablets.

Factorial design:

Based on the results of preliminary trails (TD 1A to TD 3B) taken above, it was observed that both macrogol cetostearyl ether and hydroxymethyl propyl cellulose were found to increase the drug release. Hence a randomized, two level, three center point fractional factorial design of experiments was planned with below factors.

Table 2: Summary of factors used in design of experiment.

Factor	Name	Units	Minimum	Maximum	Coded Low	Coded High
A	Sodium Starch Glycolate (Intragranular)	mg	20	30	-1 ↔ 20.00	+1 ↔ 30.00
B	Macrogol cetostearyl ether (Intragranular)	mg	10	20	-1 ↔ 10.00	+1 ↔ 20.00
C	HPMC (Intragranular)	mg	2.5	5	-1 ↔ 2.50	+1 ↔ 5.00
D	HPMC (Binder solution)	mg	4	8	-1 ↔ 4.00	+1 ↔ 8.00
E	Sodium Starch Glycolate (Extra granular)	mg	15	30	-1 ↔ 15.00	+1 ↔ 30.00

Manufacturing process for Design of Experiment Batches

Lactose anhydrous, Mannitol, Hydroxypropyl methylcellulose and Sodium Starch glycolate were sifted through 40# mesh and added into rapid mixer granulator and dry mixed for 10 minutes at slow speed. Hydroxypropyl methylcellulose and Macrogol cetostearyl ether are added to purified water under stirring to form a clear solution. Tadalafil API was added to above macrogol cetostearyl ether and Hydroxypropyl methylcellulose solution and homogenized to form a uniform dispersion and was used to granulate the dry mix (Lactose anhydrous, Mannitol, Hydroxypropyl methylcellulose and Sodium Starch glycolate). The wet granules were dried at 60°C inlet temperature. The dried granules were sifted through 40# mesh. Mannitol, Sodium Starch glycolate and Colloidal silicon dioxide were sifted through 40# mesh and add to sifted dried granules and blended for 10 min. Magnesium Stearate sifted through 60 mesh was added into prelubricated blend and continued blending for 5 min and then compressed into tablets.

Table 3: Formulation composition of design of experiment batches

Ingredients	**TD4**	**TD5**	**TD6**	**TD7**	**TD8**	**TD9**	**TD10**	**TD11**	**TD12**	**TD13**
Lactose anhydrous	120.00	120.00	120.00	120.00	120.00	120.00	120.00	120.00	120.00	120.00
Mannitol	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00
Hydroxypropyl methyl cellulose	2.50	3.75	2.50	2.50	5.00	5.00	5.00	2.50	2.50	3.75
Sodium Starch glycolate	30.00	25.00	20.00	20.00	30.00	30.00	20.00	20.00	30.00	25.00
Tadalafil	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Hydroxypropyl methyl cellulose	4.00	6.00	8.00	4.00	4.00	8.00	8.00	4.00	8.00	6.00
Macrogol cetostearyl ether	20.00	15.00	20.00	20.00	20.00	10.00	20.00	10.00	10.00	15.00
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	qs	qs	qs	qs
Extra granular										
Mannitol	44.00	58.25	50.00	69.00	56.50	62.50	62.50	64.00	50.00	58.25
Sodium Starch glycolate	30.00	22.50	30.00	15.00	15.00	15.00	15.00	30.00	30.00	22.50
Collodial silicon dioxide	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Magnesium stearate	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Total	300.00	300.00	300.00	300.00	300.00	300.00	300.00	300.00	300.00	300.00

Table 4: Formulation composition of design of experiment batches

Ingredients	**TD14**	**TD15**	**TD16**	**TD17**	**TD18**	**TD19**	**TD20**	**TD21**	**TD22**
Lactose anhydrous	120.00	120.00	120.00	120.00	120.00	120.00	120.00	120.00	120.00
Mannitol	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00
Hydroxypropyl methyl cellulose	5.00	2.50	5.00	2.50	2.50	5.00	5.00	3.75	5.00
Sodium Starch glycolate	20.00	30.00	20.00	30.00	20.00	30.00	20.00	25.00	30.00
Tadalafil	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Hydroxypropyl methyl cellulose	4.00	4.00	8.00	8.00	8.00	4.00	4.00	6.00	8.00
Macrogolcetostearyl ether	10.00	10.00	10.00	20.00	10.00	10.00	20.00	15.00	20.00
Purified water	qs	qs	qs	qs	qs	qs	qs	qs	qs
Extra granular									
Mannitol	76.50	69.00	57.50	55.00	75.00	51.50	51.50	58.25	37.50
Sodium Starch glycolate	15.00	15.00	30.00	15.00	15.00	30.00	30.00	22.50	30.00
Collodial silicon dioxide	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Magnesium stearate	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Total	300.00	300.00	300.00	300.00	300.00	300.00	300.00	300.00	300.00

Physical evaluation of tablet blend and tablets.

The lubricated blend was evaluated for Bulk Density, Tapped Density, Hauser ratio and Compressibility Index.

RESULTS AND DISCUSSIONS.

The physical properties of Tadalafil API indicated that it has a poor flow.

Table 5 : Physical Properties of Tadalafil API

Bulk Density (BD)	0.26 ± 0.07 g/ml
Tapped Density (TD)	0.44 ± 0.04 g/ml
Compressibility Index (CI)	40.9 ± 0.76 %
Hausner Ratio (HR)	1.69 ± 0.21

A drug substance is considered highly soluble when the highest dose strength is soluble in < 250 ml water over a pH range of 1.2 to 6.8.The highest dose of Tadalafil is 20 mg.

Table 6: Solubility of Tadalafil API in different medium

Buffer at different pH	Solubility (mg/250ml)
0.1 N HCl	0.61 ± 0.025
Acetate Buffer pH 4.5	0.64± 0.036
Phosphate Buffer pH 6.8	0.59 ±0.012
Phosphate Buffer pH 7.4	0.64 ±0.027
Water	0.69 ±0.037

The solubility studies indicate that only 0.59 to 0.69 mg is soluble in 250 ml of aqueous media at different pH. Hence it is concluded that Tadalafil has poor solubility in aqueous media and has pH independent solubility.

Table 7: Dissolution studies of Marketed product.

Time (min)	Marketed product (% Drug Dissolved) Paddle, 1000 mL, 50 rpm,				
	0.1N HCl pH(1.2)	Phosphate Buffer (pH 4.5)	Phosphate Buffer (pH 6.8)	Purified Water	Water with 0.5% SLS
5	11±4.9	11 ±4.1	9 ±3.9	16±2.9	24±3.1
10	12 ±2.4	14±1.5	11 ±1.2	19 ±3.5	41 ±0.8
20	13 ±2.1	14 ±1.9	12 ±0.9	20 ±3.8	56 ±1.4
30	14 ±1.9	16 ±1.7	14 ±1.7	20 ±2.5	79 ±1.9
45	15 ±2.1	16 ±2.1	17±2.6	21 ±2.4	82 ±2.1
60	16±2.3	17±2.2	17±1.8	22±2.9	97±3.0

The dissolution studies performed on marketed product indicates that there is incomplete release of Tadalafil in pH 1.2 to 6.8, while there is complete release when surfactant is added. This indicates that solubility of Tadalafil increases in presence of surfactant

Table 8: Physicochemical properties of formulation compositions (Mean Values)

Ingredients	TD4	TD5	TD6	TD7	TD8	TD9	TD10	TD11	TD12	TD13
Bulk Density	0.51	0.52	0.54	0.52	0.53	0.55	0.52	0.57	0.52	0.55
Tapped density	0.66	0.66	0.68	0.67	0.64	0.7	0.68	0.68	0.67	0.69
Hausner ratio	1.29	1.27	1.26	1.29	1.21	1.27	1.31	1.19	1.29	1.25
Compressibility Index (%)	22.73	21.21	20.59	22.39	17.19	21.43	23.53	16.18	22.39	20.29
Assay (%)	100.4	98.8	102.1	100.1	99.2	99.7	99.1	101.2	102.4	100.8
Disintegration (sec)	156	152	139	141	154	158	162	157	161	149
Hardness (Kp)	5.4	6.2	5.9	5.1	5.8	6.1	5.9	6.4	5.1	5.9

Table 9: Physicochemical properties of formulation compositions (Mean Values)

Ingredients	TD14	TD15	TD16	TD17	TD18	TD19	TD20	TD21	TD22
Bulk Density	0.51	0.52	0.5	0.53	0.55	0.54	0.51	0.52	0.53
Tapped density	0.65	0.66	0.64	0.64	0.63	0.64	0.66	0.64	0.68
Hausner ratio	1.27	1.27	1.28	1.21	1.15	1.19	1.29	1.23	1.28
Compressibility Index (%)	21.54	21.21	21.88	17.19	12.70	15.63	22.73	18.75	22.06
Assay (%)	99.1	98.9	99.7	99.6	100.2	101.4	102.8	100.7	100.2
Disintegration (sec)	151	149	154	157	162	152	149	154	149
Hardness (Kp)	6.1	5.4	5.9	5.7	6.0	5.4	5.7	5.2	5.9

Table 10: Dissolution profile in USP dissolution media, water with 0.5 % SLS, 50 RPM, Paddle 1000 ml.

Time point	Marketed Product	TD1A	TD1B	TD2A	TD2B	TD3A	TD3B
5 min	24.0	23.0	29.0	26.0	28.0	35.0	39.0
10 min	41.0	42.0	49.0	44.0	52.0	59.0	68.0
20 min	56.0	68.0	75.0	64.0	79.0	82.0	89.0
30 min	79.0	77.0	82.0	75.0	85.0	87.0	95.0
45 min	82.0	82.0	86.0	84.0	91.0	90.0	98.0
60 min	97.0	91.0	94.0	94.0	97.0	92.0	99.0

The dissolution profile of marketed product is less than that of test formulations. It is observed that with wet granulation process, increased release of drug was observed. Going further with the design of experiment study plan, trails were executed higher drug release in 10 minutes. The composition and result of design studies is shown in below table.

Table 11: Design layout and response for designed formulations

Batch No	Std	Run	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Response 1
			A:SSG (IG)	B:MCE (IG)	C:HPMC (IG)	D:HPMC (Binder)	E:SSG (EG)	Release in 10 minutes
			mg	mg	mg	mg	mg	%
TD4	4	1	30	20	2.5	4	30	89.0
TD5	19	2	25	15	3.75	6	22.5	82.0
TD6	11	3	20	20	2.5	8	30	91.0
TD7	3	4	20	20	2.5	4	15	88.0
TD8	8	5	30	20	5	4	15	82.0
TD9	14	6	30	10	5	8	15	86.0
TD10	15	7	20	20	5	8	15	92.0
TD11	1	8	20	10	2.5	4	30	83.0
TD12	10	9	30	10	2.5	8	30	87.0
TD13	18	10	25	15	3.75	6	22.5	81.0
TD14	5	11	20	10	5	4	15	86.0
TD15	2	12	30	10	2.5	4	15	76.0
TD16	13	13	20	10	5	8	30	77.0
TD17	12	14	30	20	2.5	8	15	89.0
TD18	9	15	20	10	2.5	8	15	78.0
TD19	6	16	30	10	5	4	30	81.0
TD20	7	17	20	20	5	4	30	85.0
TD21	17	18	25	15	3.75	6	22.5	82.0
TD22	16	19	30	20	5	8	30	89.0

Final Equation in Terms of Coded Factors:

% release at 10 minutes = +84.42 + 3.19B-0.18 C + 1.19 D +1.69 AD+1.31 AE+ 0.937 BD – 2.06CE.The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

Table 12: ANOVA for selected factorial model

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	340.38	6	56.73	11.69	0.0002	significant
B-MCE IG	162.56	1	162.56	33.49	< 0.0001	
D-HPMC Binder	22.56	1	22.56	4.65	0.0521	
AD	45.56	1	45.56	9.39	0.0098	
AE	27.56	1	27.56	5.68	0.0346	
BD	14.06	1	14.06	2.90	0.1145	
CE	68.06	1	68.06	14.02	0.0028	
Residual	58.26	12	4.85			
Lack of Fit	57.59	10	5.76	17.28	0.0559	not significant
Pure Error	0.6667	2	0.3333			
Cor Total	398.63	18				

The **Model F-value** of 11.69 implies the model is significant. There is only a 0.02% chance that an F-value this large could occur due to noise.**P-values** less than 0.0500 indicate model terms are significant. In this case B, AD, AE, CE are significant model

terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Table 13: Fit Statistics

Std. Dev.	2.20		**R^2**	0.8539
Mean	84.42		**Adjusted R^2**	0.7808
C.V. %	2.61		**Predicted R^2**	0.6678
			Adeq Precision	11.5898

The **Predicted R^2** of 0.6678 is in reasonable agreement with the **Adjusted R^2** of 0.7808; i.e. the difference is less than 0.2.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 11.590 indicates an adequate signal. This model can be used to navigate the design space.

Fig 1: Half normal plot for Dissolution at 10 minutes

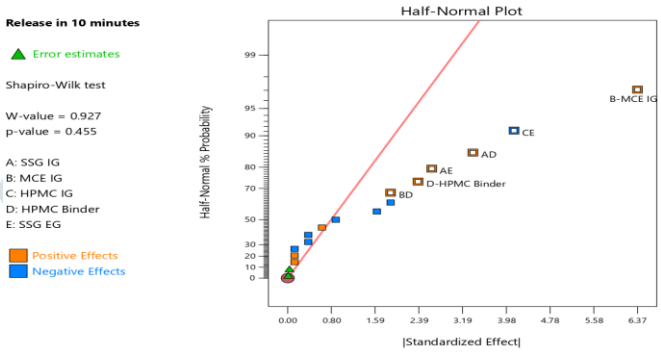
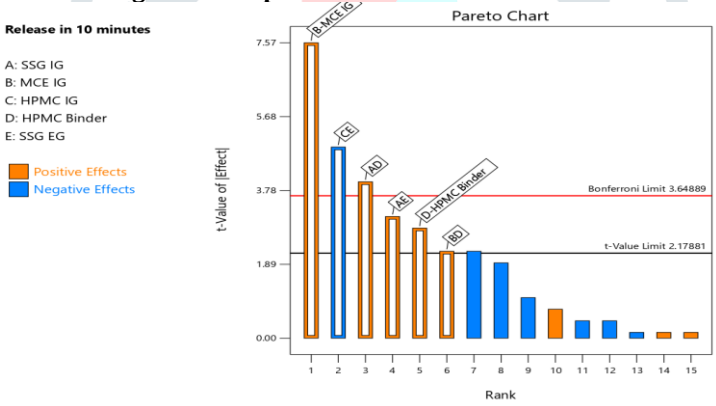
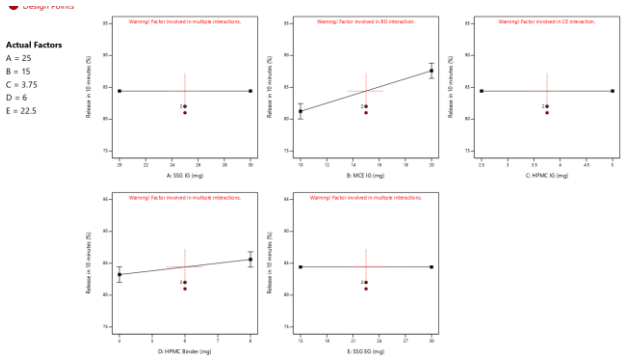


Fig 2: Pareto plot for Dissolution at 10 minutes



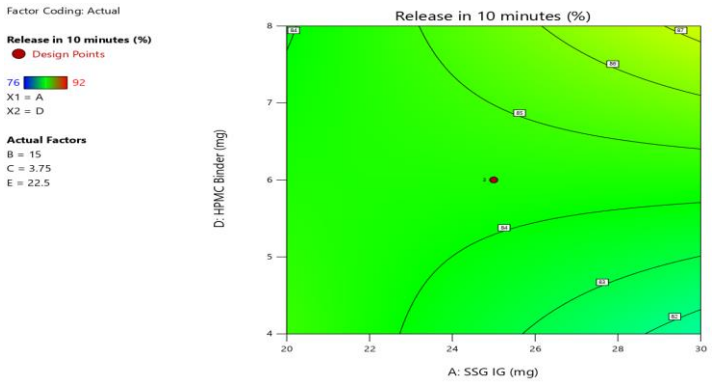
Half normal plot, Pareto chart indicates that factor macrogol cetostearyl ether contributes more to the % release , followed by interaction between CE, AD, AE, D and BD

Fig 3: One factor plot for Dissolution at 10 minutes



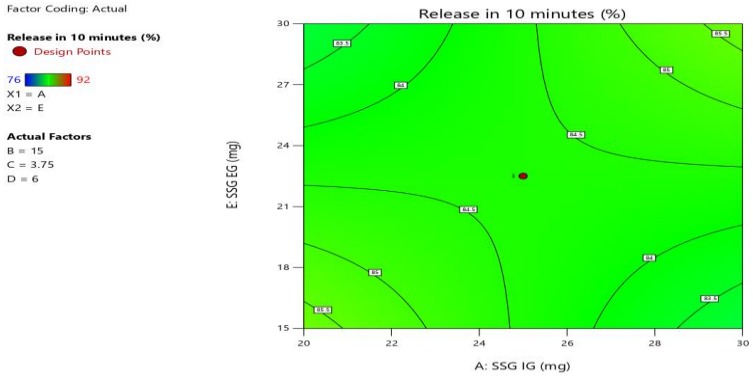
One fator plot indicates that with increase in macrogol cetostearyl ether and hydroxy propyle methyl cellulose , the dissolution increases.

Fig 4 : Contour plot for Dissolution at 10 minutes between SSG (IG) and HPMC (Binder)



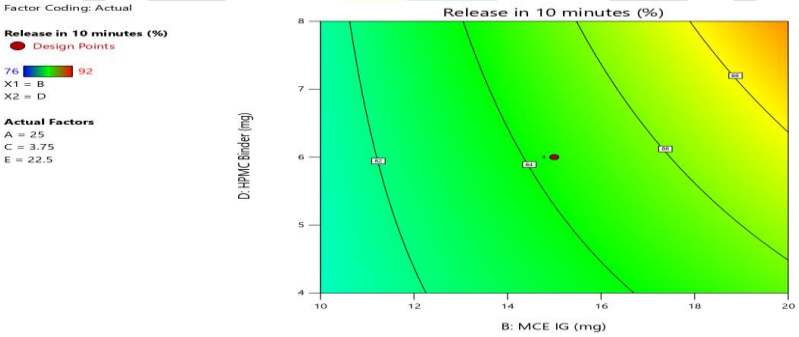
The interaction between Intragranular Sodium starch glycollate and HPMC in binder solution shows a positive impact on the drug release.

Fig 5 : Contour plot for Dissolution at 10 minutes between SSG (IG) and SSG (EG)



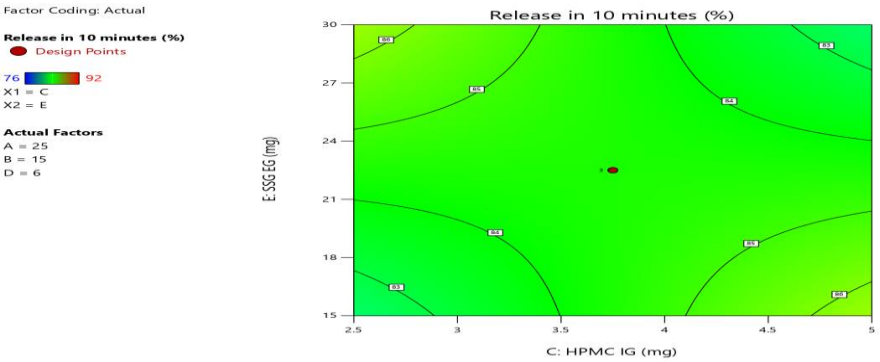
The interaction between Intragranular Sodium starch glycollate and Extra granular Sodium starch glycollate shows a positive impact on the drug release.

Fig 6: Contour plot for Dissolution at 10 minutes between MCE(IG) and HPMC (Binder)



The interaction between Macrogol cetostearyl ether and Hydroxypropyl methyl cellulose shows a positive impact on the drug release.

Fig 7: Contour plot for Dissolution at 10 minutes between SSG (IG) and HPMC (IG)



The interaction between Hydroxypropyl methyl cellulose in Intragranular portion and Extra granular Sodium starch glycollate shows a negative impact on the drug release.

Fig 8 : XRD of Tadalafil API

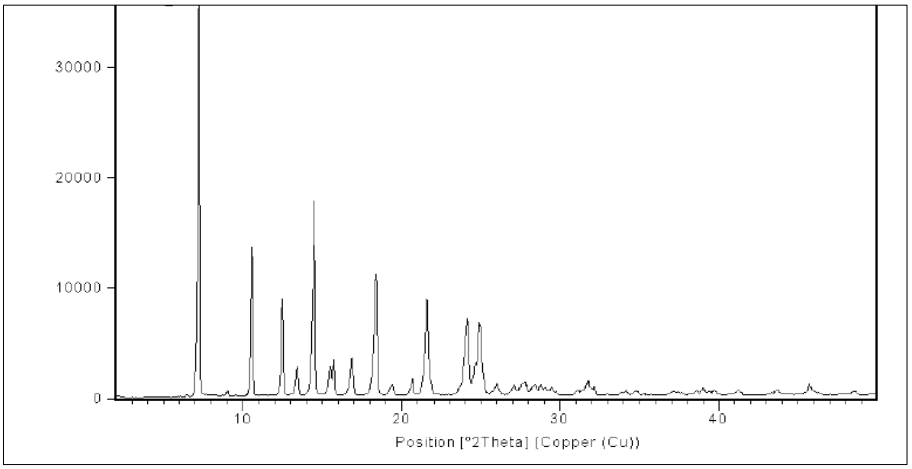


Fig 9 : XRD of Tadalafil final formulation (TD10)

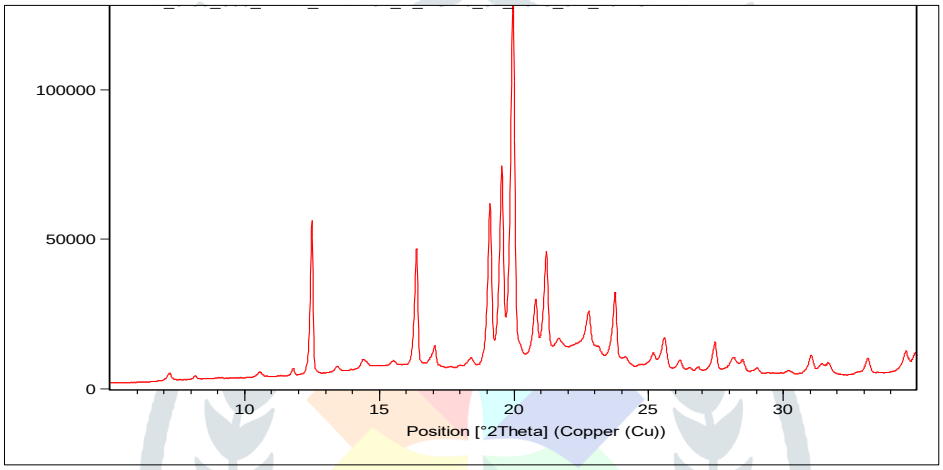
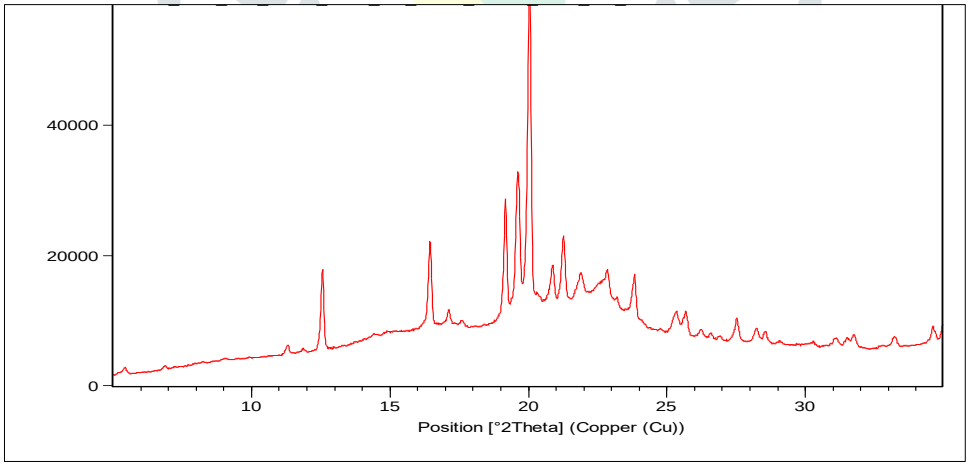


Fig 10 : XRD of Placebo Tablet



In Tadalafil API, characteristics peaks are observed at 2 theta 7.3±0.2° and 18.5±0.2°.The same characteristic peaks were observed in finalized formulation TD10 . Rests of the API peaks were interfering with placebo peaks. This indicates that crystallinity of Tadalafil is retained in the formulation.

CONCLUSION:

In present study, a simple wet granulation process was tried with varying amounts of polymers. The dissolution rate was found to be significantly enhanced with marketed product. One fator plot indicates that with increase in macrogol cetostearyl ether and hydroxy propyle methyl cellulose , the dissolution increases. The interaction between Intragranular Sodium starch glycollate and

HPMC in binder solution shows a positive impact on the drug release. The interaction between Intragranular Sodium starch glycollate and Extra granular Sodium starch glycollate shows a positive impact on the drug release. The interaction between Macrogol cetostearyl ether and Hydroxypropyl methyl cellulose shows a positive impact on the drug release. The interaction between Hydroxypropyl methyl cellulose in intragranular portion and extra granular Sodium starch glycollate shows a negative impact on the drug release. Maximum drug release was obtained for formulation TD10. All the physical properties were satisfactory. pXRD studies reveled that crystallinity of drug product is retained.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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