Research Article

Formulation and Optimisation of Immediate Release Dosage Form of Efavirenz Using Design of Experiments

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ABSTRACT

The main goal of this study was to develop a stable formulation of Efavirenz as an immediate release tablet using design of experiments. Tablets were prepared by using wet granulation method. A 3^2 Central Composite Design (CCD) was selected to optimize the formulation of the varied response variable (Dissolution). The two factors Croscarmellose Sodium and HydroxyPropyl Cellulose were determined as the critical material attributes from preliminary studies and varied as required by the experimental design. The screened factors of overlay plot were incorporated into a suitable experimental design to optimize the process formulation. A 2^2 factorial design (FD) was selected to screen the process formulation .The two factors Water Uptake and Hardness were varied as required by the experimental design. *In-vitro* % drug release Q15, Q30 and Q45 were taken as response variable. A design space was created using desired levels of response variables and a composition was selected as optimized formulation, which is compared with the marketed formulation for similarity factor. The results revealed that dissolution rate was found to be directly proportional to concentration of disintegrant and inversely proportional to concentration of binder, hardness and % water uptake (w/w).

Keywords: Critical Material attributes, Experimental Design, Response Variable, Wet granulation.

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery. However, several orally administered drugs have reduced bioavailability due to poor water solubility. In biopharmaceutical classification system drugs with low aqueous solubility, slow dissolution rate, high dose, and high membrane permeability are categorized as Class II drug. To overcome low bioavailability, many of the modern oral drug delivery systems emphasize on formulation strategies such as alteration of solvent composition, carrier systems as well as chemical and physical modifications.[1,2]

Efavirenz (EFV) is an antihuman immunodeficiency virus (antiHIV) drug that works by inhibiting the non-nucleoside reverse transcriptase of HIV and is used as a part of the highly active antiretroviral therapy. EFV is freely soluble in methanol, but it is practically insoluble in water (4 µg/ml) and has a bioavailability of 40 to 45%.[3]

Modern optimization techniques using experimental designs play important role in formulation development, as they help in developing the best possible formulation under a given set of conditions, thus saving considerable time, money and developmental effort.[4,5] These systematic techniques are known to provide in depth understanding and ability to explore and defend the ranges for varied formulation and processing factors. Central composite design (CCD), in this regard, has been frequently employed for the optimization of immediate release formulations. Current investigations aim at developing immediate release dosage form by using CCD optimization technique.

MATERIALS AND METHODS

Materials

Efavirenz (Mylan Laboratories, Hyderabad), Microcrystalline cellulose or Avicel, Croscarmellose sodium or Acdisol (FMC biopolymer), Lactose Monohydrate or Flowlac100 (Colorcon), Hydroxy propyl Cellulose or Klucel (BASF), Sodium Lauryl Sulphate (ISP), Magnesium Stearate (Ferro).

Methods

Screening of polymers and their levels

During preliminary studies, all the excipients Avicel PH 101 (Filler), Klucel Exf (Binder), Flowlac 100 (Diluent), Acdisol (Disintegrant), Avicel PH102, Sodium Lauryl Sulphate (Surfactant) were investigated at different concentrations to determine the critical material attributes. Later on, depending on the results obtained, the blend containing Acdisol and Klucel EXF and their levels were selected for further investigation.

Formulation of tablets as per the experimental design, CCD

Experimental Design

A central composite design (CCD) for two factors at three levels each (with α=1), equivalent to a 3^2 factorial design [13 experiments], was selected to optimize varied response variables. The two factors viz. Hydroxy Propyl Cellulose (Klucel EXF) & Croscarmellose Sodium (Ac-di-sol) were varied, as required by the experimental design, and the factor levels suitably coded. Quantity of filler (MCC)

was adjusted so as to keep the tablet weight constant (1100 mg).

Table 1: Factor combinations as per chosen experimental design, CCD

Run (Trials)	Ac-di-sol	Klucel EXF
1	+	+
2	+	0
3	+	-
4	0	+
5	0	0
6	0	-
7	-	+
8	-	0
9	-	-
10	0	0
11	0	0
12	0	0
13	0	0

Translation of coded levels in actual units

Croscarmellose Sodium			Hydroxy Propyl Cellulose (Exf)		
-1	0	+1	-1	0	+1
40	50	60	15	20	25

Different tablet formulations were formulated using varying amounts of polymers such as Acdisol and Klucel Exf. Sodium Lauryl Sulphate as Surfactant, Magnesium Stearate as Lubricant as shown in Table 2. Prior to use, Efavirenz is screened through #12 ASTM and all the excipients, viz. MCC PH 101, CCS, HPC, Flowlac100, SLS were screened through # 40 mesh sieve the materials were accurately weighed and mixed intimately in a polythene bag for 10 minutes. 32% Water is added slowly with continuous mixing until formation of granules. Wet Granules are sifted with mesh size #14ASTM are then kept for drying at 60^{o} C for 1hour or till the LOD comes till 1% and Intragranular granules were weighed. Croscarmellose Sodium and Micro Crystalline Cellulose PH 102(Extra granular portion) which are sifted through sieve no #40 ASTM. Magnesium stearate being a lubricant was sifted through sieves no #60ASTM is mixed with the extra granular portion which are again mixed with the intra granular portion. The blended mix was subsequently compressed into 1100 mg tablets using (18.0*8.30 mm) single-punch tablet compression machine (CADMACH).

Evaluation

In-vitro drug release study

Dissolution studies were carried out for all the tablet formulations, employing USP paddle apparatus at 50 rpm and 37 ± 0.5^{o}C, using 2%SLS as the dissolution medium[6]. An aliquot of sample was withdrawn periodically at suitable time intervals and volume was replaced with plain buffer medium. Samples were analyzed spectrophotometrically at 248nm. Drug release data obtained during *in-vitro* dissolution studies were analyzed using UV spectrophotometer, Model SHIMADZU.

Physical Evaluation

Tablets were also evaluated for hardness using an electronic hardness tester (n = 6), friability using Roche friabilator (n = 10), weight variation using Analytical balance (n = 10), and thickness using Vernier Callipers (n = 10).

Comparison of drug release with Marketed Formulation

Drug release profile of the optimized formulations was compared with marketed formulations, Sustiva, each containing 600mg of Efavirenz per tablet.

RESULTS AND DISCUSSION

Selection of polymers and excipients

Two polymers viz. CCS and HPC were selected for the preliminary studies, owing to their reported potential of release rate, non-toxicity, non-irritancy, and compatibility with drug. Dissolution parameters of the two polymers were studied by formulating them into tablet dosage form. CCS was found to be the most promising in regulating the drug release profile as a disintegrant, followed by HPC which is a binder with moderate viscosity for immediate release. The successful use of the polymer combination of CCS and HPC has already been documented in various literature reports in attaining excellent immediate release.

Water insoluble excipient with lower density such as MCC is used as diluent.[12] Flowlac 100 is used as filler. Stepanol is used as surfactant to increase the bioavailability of the dosage form. Selection of concentration of MST as ~1% was based on earlier studies carried out in our laboratories as it was found to be the adequate concentration to attain good powder flow characteristics and die ejection.[5] The same was ratified in our preliminary experimental studies too.

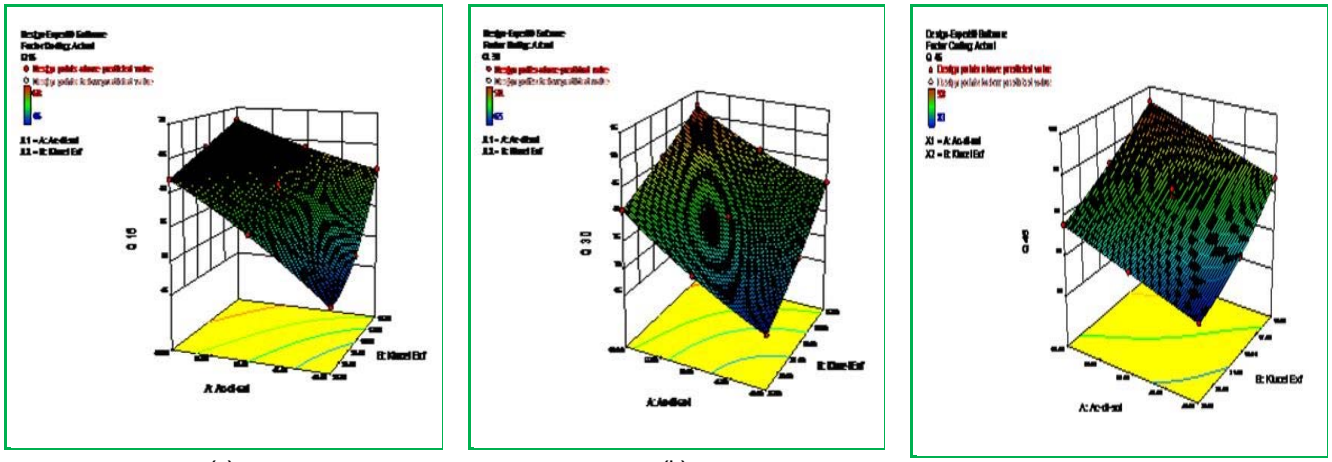
Physical Evaluation

Tablet weights varied between 11.009 and 11.016 mg, and thickness between 7.43 and 7.46 mm (7.44 ± 0.2 mm). Tablets require a certain amount of strength or hardness, and resistance to friability, to withstand the mechanical shocks of handling during their manufacture, shipping and packaging. The hardness of a tablet is closely related to its disintegration time and dissolution, and eventually its drug release rate.[9] Tablet hardness monitoring, therefore, is especially important for drug products which possess real or potential bioavailability problems or those sensitive to altered dissolution release profiles as a function of the compressive force applied. Representative tablets tested from each batch possessed hardness values ranging between 15-18Kp, indicative of adequate strength to provide good tablet disintegration and dissolution profiles and to prevent friability losses. All

the tablets tested from each batch exhibited friability values ranging between 0.292% and 0.310% w/w (0.300 ± 0.10%), far less than the limit of 1% w/w, generally considered as acceptable by the official compendia.[10,11]

Table 2: Composition of Efavirenz Tablets

Ingredients	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
Efavirenz	600	600	600	600	600	600	600	600	600	600	600	600	600
AvicelPH 101	201	221	216	211	216	221	221	221	226	216	216	216	216
Flow lac 100	50	50	50	50	50	50	50	50	50	50	50	50	50
Ac - di-sol	30	30	30	25	25	25	20	20	20	25	25	25	25
Klucel EXF	25	20	15	25	20	15	25	20	15	20	20	20	20
Stepanol WA100 (SLS)	25	25	25	25	25	25	25	25	25	25	25	25	25
Water Uptake (%)	32	32	32	32	32	32	32	32	32	32	32	32	32
Ac - di-sol	30	30	30	25	25	25	20	20	20	25	25	25	25
AvicelPH 102	127	132	122	127	127	127	127	132	132	127	127	127	127
Magnesium stearate	12	12	12	12	12	12	12	12	12	12	12	12	12
Total	1100	1100	1100	1100	1100	1100	1100	1100	1100	1100	1100	1100	1100



(a) (b) (c)

Figure 1: (a) 3D graph showing the influence of CCS and HPC on %Drug release at Q15 level; (b) 3D graph showing the influence of CCS and HPC on %Drug release at Q30 level; (c) 3D graph showing the influence of CCS and HPC on %Drug release at Q45 level.

Conclusion: The 3D graph for Q15, Q30 and Q45 indicates that at low levels of Klucel Exf and high levels of Ac-di-sol, *in-vitro* drug release increases and at high levels of Klucel Exf and low levels of Ac-di-sol, in-vitro drug release decreases.

In-vitro drug release studies

In the present study, Table 5 enlists various dissolution profiles. A total number of 19 trials were prepared. When drug release profiles of formulations (F1-F13) were carried out to select the optimized formulation based on Central Composite Design. F5, F10, F11, F12 and F13 showed normal drug release due to the medium levels of both the disintegrant (Ac-di-sol) and the binder (Klucel EXF). F6 and F3 showed higher drug release with respective to other formulations as this could be because of higher level of disintegrant and lower level of binder. F1, F4, F7 and F8 showed comparatively slower release due to the high level of binder. The dissolution rate was found to be directly proportional to concentration of disintegrant (Ac-di-sol) and inversely proportional to concentration of binder (Klucel EXF).

Based on drug release profiles of all the trials, Overlay plot of CCD suggested a design space with some approximation of the drug release profiles for desirable formulation which trial 14 i.e., F14 is prepared. The drug release profile of F14 was found to be of satisfactory result and F14 formulation is found to be optimum and was further optimized for water uptake and hardness range for process optimization and a total of 4trials were prepared (F15-F18) based on Factorial Design. F18 showed lower drug release as it has higher water uptake as well hardness range. F15 has higher drug release as it has lesser water uptake and hardness range. F16 and F17 has almost equal drug release as it has lesser water uptake and higher hardness range and vice versa. Based on drug release profiles of all the trials, Overlay plot of FD suggested a design space with some approximation of the drug release profiles for desirable formulation which trial

19 i.e., F19 is prepared. The drug release profile of F19 was found to be of satisfactory result. And it is found to be matching with the drug release profile of the innovator.

Statistical analysis and conclusion

Values of "Prob > F" less than 0.0500 indicate model terms are significant. The "P" values for all four responses ranging from 0.001 to 0.0024 as well as The "R^2" values for all four responses ranging from 0.9841 to 0.9966 vouch high prognostic ability of the RSM polynomials. Eight coefficients (β_1 to β_8) were calculated with β_0 representing the intercept, and β_3 to β_8, representing the various quadratic and interaction terms (Eq).

Eq. $Y = \beta_0 + \beta_1 X1 + \beta_2 X2 + \beta_3 X1 X2 + \beta_4 X1^2 + \beta_5 X2^2 + \beta_6 X1^2 X2 + \beta_7 X1 X2^2 + \beta_8 X1^2 X2^2$

Various response surfaces are depicted in figures No 1(a) (b) and (c) portray the 3-D response surface plots. Fig no 1(a) (b) and (c) depicts increasing trend in the values of Q at initial period (Q 15 min) with increments of Ac-di-sol at lower klucel EXF concentrations. A quite linear decreasing trend in Q values with augmentations of klucel EXF fractions has been observed.

The influence of Ac-di-sol is distinctly far more significant at lower concentrations of Klucel EXF, indicating that the later has better release altering properties. However at higher concentrations of Klucel EXF the influence of disintegrant to become insignificant.

Table 3: Composition of Optimized Batch of formulation based on Overlay Plot

Ingredients	Trial 14 Mg/Tab
Intra granular part	
Efavirenz- B form	600
Avicel PH 101	215
Flow lac 100	50
Ac - di-sol	24
Klucel EXF	22
Sodium Lauryl Sulpahte	25
Extra granular part	
Ac - di-sol	24
Avicel PH 102	128
Magnesium stearate	12
Total weight	**1100**

The Suggested quantitative formula was further optimized for Process Optimization.

By placing the *in-vitro* dissolution data and the formulation optimization trials, the Overlay plot indicates a design space for desirable formulation with a prediction of 55%, 73% and 89% at Q15, Q30 and Q45 level. The design space suggested a composition of Acdisol (48mg) and Klucel (22mg). F14 Trial is carried out by keeping the other excipients constant and changing the concentration of Acdisol and Klucel which gave satisfactory result and therefore considered as optimized formulation.

Process Optimization of Optimized Formula

In the design of experiment approach process parameters such as hardness, water uptake is considered as process variables. They help in understanding the effect of unit operation on product quality.[7,8] Hardness was selected and further studies were carried out at different hardness ranges.

Physical parameters and dissolution studies were carried out for selected hardness ranges. A full factorial design (FD) for two factors at two levels were selected to screen the varied response variable. The two factors viz. Hardness and Water Uptake were varied as required by the experimental design and the factor levels.

Table 4: Factor combinations as per chosen experimental design, FFD

Water Uptake (%w/w)		Hardness (kp)	
-1	+1	-1	+1
15	40	13	23
Trial/ RUN	**Water Uptake (%w/w)**	**Hardness (kp)**	**Water Uptake (%w/w)**	**Hardness (kp)**
15	-	-	15	13
16	-	+	15	23
17	+	-	40	13
18	+	+	40	23

Statistical analysis and conclusion:

The R^2 Values of 1.0000 implies the model is significant. Release rate was found to be inversely proportional to the hardness and % w/w water uptake.

Eight coefficients (β_1 and β_2) were calculated with β_0 representing the intercept, and β3 representing the interaction term (Eq.).

Eq. $Y = \beta_0 + \beta_1 X1 + \beta_2 X2 + \beta_3 X1 X2$

Various response surfaces are depicted in figures No 3(a), (b) and (c) portray the 3-D response surface plots. Depicts decreasing trend in the values of Q at with increments of Hardness at as well as water uptake. The influence of water uptake is distinctly far more significant as compared to hardness. At lower water uptake levels, effect of hardness found to be less significant.

By placing the *in-vitro* dissolution data and the process optimization trials based on table 4, Overlay plot indicates a design space for desirable formulation with a prediction of 55%, 68% and 85% at Q15, Q30 and Q45 level. The design space suggested a water uptake of 38% and hardness of 14-15kp. F19 Trial is carried out with table 3 composition and pres satisfactory result and therefore considered as optimized formulation.

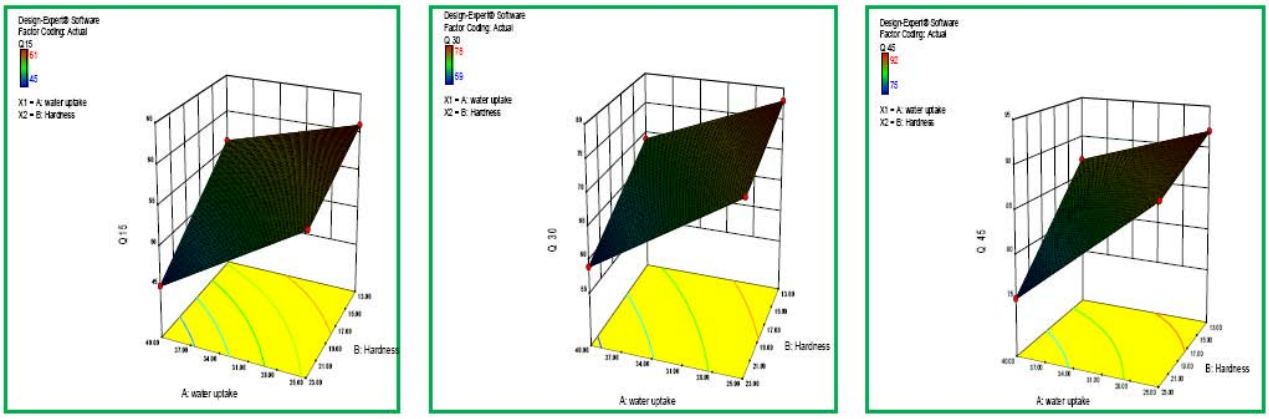


Figure 2: (a) 3D graph showing the influence of Water uptake and hardness on %Drug release at Q15 level
(b) 3D Graph showing the influence of Water uptake and hardness on %Drug release at Q30level
(c) 3D graph showing the influence of Water uptake and hardness on %Drug release at Q45level.

Table 5: *In-vitro* Dissolution of Batches F1-F19 with Comparison of Reference versus Test Product

Time (Min)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}	F_{15}	F_{16}	F_{17}	F_{18}	F_{19}	Coated F_{19}(Test)	Reference (Sustiva)
10	38	41	46	34	37	42	28	39	41	38	37	38	37	37	38	35	35	25	40	32	31
15	62	65	68	55	58	64	46	50	61	59	60	57	60	58	61	56	56	45	55	47	45
30	81	86	92	72	74	85	65	72	81	77	76	76	76	73	78	73	69	59	66	58	53
45	89	93	98	86	90	95	83	86	92	91	90	92	91	87	92	88	87	75	86	87	86
60	97	98	99	98	97	97	98	98	98	98	97	99	97	98	98	97	97	97	98	99	99
																				F2 (Similarity factor)	78

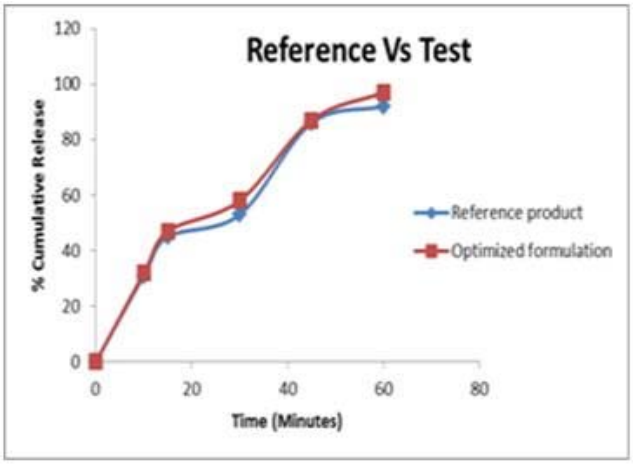


Figure 3: Comparison of Reference versus Test Product

Drug release from the optimized formulation was found to be closer to that of Sustiva. Similarly, the release parameters were quite close to each other. Further, the values of similarity factor unambiguously corroborating the sameness of the release profiles. Fig. 3 portrays the respective release profiles of the marketed formulations (Sustiva) and optimized formulation superimposed over each other also indicating almost analogy of release performance with each other. Thus, the studies conclude successful development of IR Tablet of Efavirenz maintaining similar drug release profiles as observed with the marketed products.

CONCLUSION

Efavirenz is designed as immediate release dosage form so as to release the drug instantly to inhibit HIV replication. As, the pure drug is very fluffy the formulations were prepared by wet granulation using HPC as a binder and to CCS is used as disintegrant to disintegrate quickly. CCS is used in the intra and extra granular part to make use of the swelling and wicking action and SLS as a surfactant to improve the bioavailability. In order to optimize the dosage form, only systematic studies using DoE optimization could surmount this hiccup of balancing optimal composition using this polymer combination. The choice of experimental design, i.e., a 2-factor CCD and FD, was found to be highly appropriate, as it can detect any non-linearity in factor-response relationship with minimal expenditure of developmental effort and time. The optimized formulation exhibited excellent drug release vouching the success of the experimental approaches followed. Besides identical drug release profile to that observed with the marketed formulations.

From this study, it was concluded that optimized levels of binder (Hydroxy Propyl Cellulose) 21-24 mg/ tablet and superdisintegrant (Croscarmellose sodium) 48mg/tablet and process optimizing with water uptake 38% and hardness (13-16kp)are imperative to acquire maximum in vitro % drug release. The study offers a platform technology, the results of which can be successfully extrapolated to other molecules too.

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