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Research article

Application of D-optimal mixture design for optimization of production parameters of fast and complete release dexamethasone amorphous solid dispersion tablet

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Key words: Solid dispersion, Dissolution, Solubility, Bioavailability, Oral absorption, Mixture Design.

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Abstract

Dexamethasone is a glucocorticoid used widely worldwide for immunosuppressive treatment, allergies, bronchiolitis, and croup, among others. However poor aqueous solubility (0.1mg/ml) leads to poor rate of dissolution and hence limits its oral bioavailability. The objective of the present study was to optimize the level of different formulation components like PEG-6000 (hydrophilic carrier), lactose (filler) and starch (disintegrating agent) for the development of fast and complete release tablet of dexamethasone by 16 run D-Optimal Mixture Design. Dexamethasone was dispersed in PEG-6000 by Melt/Fusion method. FTIR and DSC study confirmed that dexamethasone was compatible with PEG-6000 and upon dispersion it became amorphous. Tablets were prepared by direct compression method. UV Spectrophotometric method was developed for estimation of dexamethasone. Both the response parameters Maximum % Drug Released (MDR) and Time to Maximum % Drug Release (T_{MDR}) were best fitted to Cubic Mixture Model. The optimized tablet released 99.5% drug in 5 minute.

Introduction

Oral route is the easiest way for delivery of drugs. However oral delivery of poorly water soluble drugs often results in poor bioavailability because the absorption process becomes dissolution rate limited [1]. Thus, many pharmacologically active molecules become unsuitable for clinical use as a result of their limited solubility and poor rate of dissolution leading to poor bioavailability [2,3]. So, there is a need to develop formulation strategies for fast and complete dissolution of orally administered drug molecules. One such approach may be to disperse the drug molecule in a hydrophilic solid matrix, before compression into tablet.

Dexamethasone, a synthetic adrenocortical steroid, is designated chemically as 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene,3,20-dione. It is 25 times more potent than cortisol regarding its glucocorticoid effect while it has minimal mineralocorticoid effect. Pharmacologically dexamethasone has anti-inflammatory and immunosuppressant effects. So clinically it is used mainly for the treatment of conditions including endocrine disorders, allergic states, dermatologic problems, gastrointestinal disorder, hematologic disorders, renal diseases, respiratory diseases, rheumatic disorders and a number of infectious disorders. In preterm labor it may be used to improve outcomes in the baby. But the drug is practically insoluble in water leading to poor and irregular bioavailability when administered orally [4]. This is the main problem in its clinical use. Also the therapeutic efficacy has been further challenged for its short half-life, and potential toxicity at high doses [5].

Statistical design of experiments (DoE), a matrix-based multifactor method, does measure interaction effects and encompasses the entire multidimensional experimental region [6]. Aided by software programmes for this purpose, DoE has become recognized as an important tool for more rapid pharmaceutical process and product development [7]. Response surface methodology (RSM) is one of the well-known methods in the development and optimization of drug delivery systems. The basis of RSM is polynomial models fit by least-square regression and confirmed statistically via analysis of variance (ANOVA) [8]. By deriving empirical, but functionally useful, relationships between process responses and the critical input variables, RSM facilitates discovery of 'Sweet Spots' over the experimental domain to select the optimal formulation.

There are different types of RSM designs available, like Box Behnken design, Factorial design [9] etc. Mixture design [10] is recommended as a useful tool, when two or more components are varying, but the total amount of those ingredients is fixed. Thus Mixture design is most suitable for optimization of fixed weight tablet dosage form. Additionally, it requires fewer experimental runs and less time and thus provides a more cost effective technique than the conventional process of formulating and optimization of dosage forms.

This study aims to preparation of solid dispersion of dexamethasone in PEG-6000 and optimization of different formulation components for the development of fast and complete release tablet by 16 Run D-Optimal Mixture Design.

Experimental

Materials

Dexamethasone, Polyethylene glycol-6000 (PEG-6000) and Lactose monohydrate were obtained from Merck, India. Magnesium stearate, Talc and all other ingredients were obtained commercially and used as received.

Methods

Preparation of solid dispersion of dexamethasone in PEG-6000 by melting/fusion method

The experimental setup was consisting of a water bath on a hot plate-magnetic stirrer. A small beaker containing desired amount of PEG-6000 and dexamethasone was placed in the water bath. The melting point of PEG-6000 was found to be 60-63^{0}C. So, the temperature of water bath was adjusted to 70^{0}C. Upon melting of PEG-6000, the mixture was mixed thoroughly with magnetic stirrer at moderate speed to get a homogeneous molecular dispersion of dexamethasone in molten mass. After 20 minutes, the molten mass was allowed to cool at room temperature for solidification. On next day, the solid mass was pulverized through the sieve no: 44 and kept in desiccator till further use.

Preparation of tablet by direct compression

Starch and Lactose monohydrate were passed through sieve no: 44 and mixed with solid dispersed dexamethasone (SDD) or equivalent amount of dexamethasone by geometric dilution. Talc and Mg-stearate were added and mixed thoroughly. This final mixture was compressed into 650mg tablet. In case of tablet with dexamethasone in solid crystal form, the mass of PEG-6000 was adjusted with Lactose monohydrate.

Dexamethasone-excipients compatibility study

The FTIR analysis of dexamethasone, dexamethasone+ PEG-6000 physical mixture, dexamethasone dispersed in PEG-6000 were done by Shimadzu IR Prestige-21 FTIR Spectrometer.

Solid state property of dexamethasone after dispersion in PEG-6000

The differential thermogravimetric analysis of dexamethasone, dexamethasone dispersed in PEG-6000 (1:10), physical mixture of dexamethasone with all excipients except PEG-6000, blank tablet (without dexamethasone), tablet of dexamethasone (without PEG-6000), tablet of dexamethasone dispersed in PEG-6000 (1:10) were done with PerkinElmer Pyris Diamond Thermo-gravimetric/Differential Thermal Analyzer. Platinum crucible was used with alpha alumina powder as reference.

Designing of experiments

Designing of 16 run Randomized D-Optimal Mixture Design and analysis of experimental data were done with Design Expert® 7.1.5. There were 4 Lack-of-fit points, 4 Replicate points and 1 additional center point. The total mass of tablet was 650mg. The mass of dexamethasone, talc and Mg-stearate per tablet were fixed to be 2mg, 15mg and 25mg respectively. So, the variable factors for the designed experiments were the content of PEG-6000, Starch and Lactose with following design constraints:

Low (mg)	≤	Constraint	≤	High (mg)
20.0	≤	A: PEG-6000	≤	40.0
200.0	≤	B: Starch	≤	300.0
268.0	≤	C: Lactose	≤	388.0
A+B+C = 608.0 mg				

The details of designed experimental runs are shown in Table 1. Maximum % Drug Released and Time to release of Maximum % Drug were considered as Response Factors.

Development of analytical method

An UV-Spectrophotometric method was developed for estimation of dexamethasone in alkaline phosphate buffer (pH 6.8) as per ICH guideline (Q2R1). Optical Density (OD) of serially diluted solutions were taken at 244nm (λ_{max}) by Jasco V-630 UV-VIS Spectrophotometer. Calibration curve was constructed using Linear Regression Analysis.

In-vitro dissolution study

In vitro release of dexamethasone from tablets were studied in 900ml phosphate buffer solution (pH 6.8) at 37^{0}C and 75 rpm using USP type II dissolution test apparatus (Veego, Mumbai, India). Aliquots of 10ml were pipetted out from dissolution medium at specified time interval and were replenished immediately with same volume of fresh medium. The samples were filtered and analyzed spectro-photometrically at λ_{Max}= 244nm. The maximum % drug released and time to maximum % drug released for each tablet formulation designed were noted down.

Results and Discussion

The presence of signature peaks of dexamethasone (Figure 1) at 3473, 2937, 1618, 1392, 1271 cm^{-1} wave number in dexamethasone-PEG6000 (1:10) physical mixture (Figure 1B) and solid dispersion of dexamethasone in PEG-6000 (1:10) (Figure 1C) confirms that it is compatible with PEG-6000.

In Figure 2 Black thermogram indicates that dexamethasone was a crystalline solid that melts at 266.9 ^{0}C. There was no polymorphic form. Red thermogram has a single peak at 65.45 ^{0}C (melting point of PEG-6000). This indicates that dexamethasone was present as amorphous form when dispersed in PEG-6000. This enhances its aqueous solubility. The blue and green thermograms are identical. If we compare them with pink thermogram, then obviously, there is a dip [though not a sharp peak; as amount of dexamethasone (2 mg) was very less in comparison to the other excipients (648 mg)] at the melting point of dexamethasone. Thus, dexamethasone remains in crystalline state when compressed into tablet. Again, the yellow thermogram shows no peak beyond 250^{0}C. Thus, it is confirmed that dexamethasone remains in amorphous form upon conversion of solid dispersion into tablet; the processing of wet granulation and compression did not affect the solid-state properties of dexamethasone.

The UV-Spectral Data of Dexamethasone in Phosphate Buffer (pH 6.8) is shown in Table 2. Regression Coefficient of 0.9972 indicates a good linearity. At concentrations, more than 5 µg/ml, recovery was within 90-110%. Limit of Detection (LOD) was 0.46 µg/ml and Limit of Quantitation (LOQ) was 1.54 µg/ml.

Dexamethasone tablets prepared using either crystalline form or solid dispersion in PEG-6000 had 3 kg/cm^2 hardness (measured using Monsanto hardness tester); 0.05-0.2% friability (determined using Roche Friabilator, Veego, Mumbai, India); and 2.01±0.02 mg potency. The details of different formulations are shown in Table 1. F1 was the best formulation obtained without solid dispersion; maximum 59.1% drug was released at 5 min, after that no further enhancement was found. Formulation F2-F17 were prepared using dexamethasone dispersed in PEG-6000; these 16 runs were generated and analyzed using Design Expert® 7.1.5.

Both the response parameters 'Maximum % Drug Released (MDR)' and 'Time to Maximum % Drug Released (T_{MDR})' were best fitted to Cubic Mixture Model. The 3D Surface Plots are shown in Figure 3 and Figure 4. Final Equations in Terms of Actual Components are shown in *equation 1* and *equation 2*.

Maximum % Drug Released = -4054.6 * PEG + 17.59 * Starch - 11.74 * Lactose + 10.73 * PEG * Starch + 10.26 * PEG * Lactose-0.015 * Starch * Lactose - 0.013 * PEG * Starch * Lactose + 0.0068 * PEG * Starch * (PEG-Starch)+0.0057 * PEG * Lactose * (PEG-Lactose)- 0.00015 * Starch * Lactose * (Starch-Lactose) …….. *equation 1*

(Time to Maximum % Drug Released) ^ 1.59= -171872* PEG -296.2 * Starch +127.0 * Lactose + 444.9* PEG * Starch + 446.2 * PEG * Lactose + 0.695 * Starch * Lactose - 0.546 * PEG * Starch * Lactose +0.266 * PEG * Starch * (PEG-Starch) +0.273* PEG * Lactose * (PEG-Lactose) +0.0021 * Starch * Lactose * (Starch-Lactose)…….. *equation 2*

As *Diagnostic Tool,* Predicted vs. Actual Plot is shown in Figure 5. Closeness of the points to the *diagonal line* confirms the predictability of the developed models in the design space.

The predicted optimized formulation (99.5% dexamethasone to be released in 5 minute) had a composition of dexamethasone: 2mg, PEG-6000: 34mg, starch: 230mg, lactose: 344mg, Magnesium Stearate: 25mg and Talc: 15mg.

Table 1. Details of experimental runs. F1 contains dexamethasone in crystalline form. Formulation F2-F17 were prepared using dexamethasone dispersed in PEG-6000; these 16 runs were generated and analyzed using Design Expert® 7.1.5.

Formulation Code	A: PEG-6000 (mg)	B: Starch (mg)	C: Lactose (mg)	Magnesium Stearate (mg)	Talc (mg)	Maximum % drug released	Time to maximum % drug release (min.)
F1	0	300	308	25	15	59.10	5
F2	20	200	388	25	15	40.01	5
F3	30	300	278	25	15	82.42	10
F4	40	300	268	25	15	60.34	5
F5	35	225	348	25	15	97.47	10
F6	40	300	268	25	15	58.71	5
F7	20	250	338	25	15	99.02	5
F8	40	200	368	25	15	71.75	20
F9	40	250	318	25	15	47.04	10
F10	20	200	388	25	15	31.05	5
F11	35	275	298	25	15	62.41	45
F12	40	200	368	25	15	70.10	20
F13	30	250	328	25	15	92.12	5
F14	20	300	288	25	15	99.50	5
F15	30	300	278	25	15	84.35	10
F16	20	300	288	25	15	98.03	5
F17	25	275	308	25	15	82.90	5

Table 2. UV-Spectral Data of Dexamethasone in Phosphate Buffer (pH 6.8)

Parameter	Values
Regression Equation	Optical Density (OD) = 0.04732 x Concentration (µg/ml)+0.0023
Intercept (a)	+0.0023
Slope (b)	0.04732
S_a (Standard Deviation of Intercept)	±0.005095
S_b (Standard Deviation of Slope)	±0.000384
±tS_a (95% Confidence interval of Intercept)	-0.007982 to 0.01258
±tS_b (95% Confidence interval of Slope)	0.04655 to 0.04810
Correlation Coefficient (r2)	0.9972
Sy.x (Standard Error of Correlation coefficient)	0.01457
Residual sum of squares	$4.5x10^{-4}$

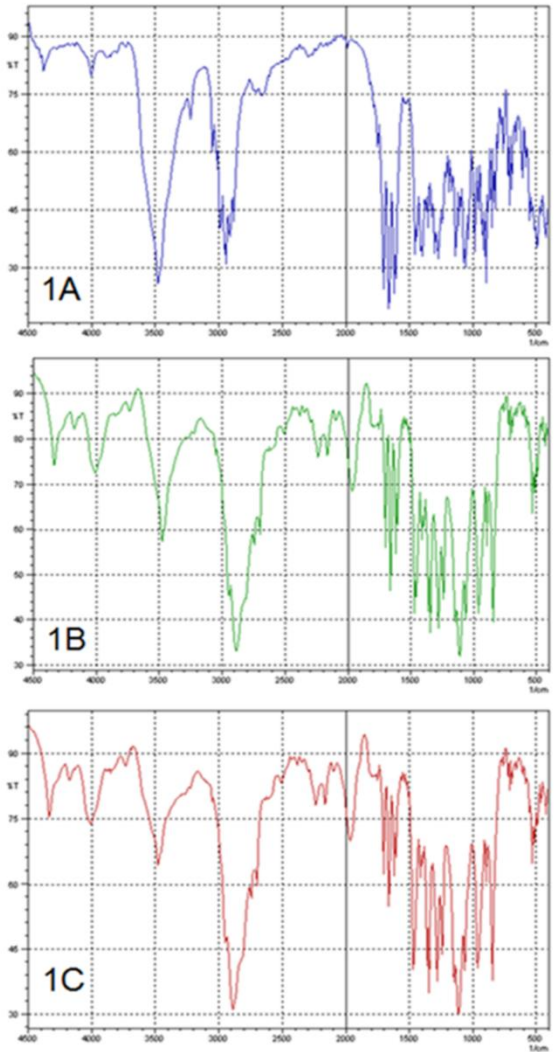

Figure 1 (A, B and C). FTIR spectra of dexamethasone (A), dexamethasone-PEG6000 (1:10) physical mixture (B), solid dispersion of dexamethasone in PEG-6000 (1:10) (C). The presence of signature peaks of dexamethasone at 3473, 2937, 1618, 1392, 1271 cm^{-1} wave number in 1B and 1C confirms that dexamethasone is compatible with PEG-6000

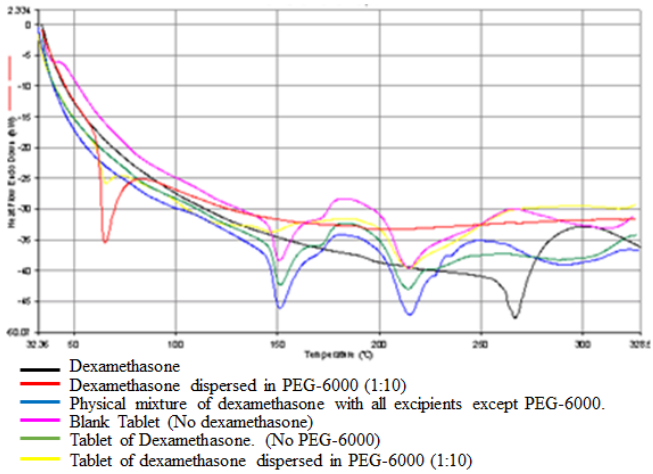

Figure 2. Black thermogram indicates that dexamethasone was a crystalline solid that melts at 266.9 ^{0}C. There was no polymorphic form. Red thermogram has a single peak at 65.45 ^{0}C (melting point of PEG-6000). This indicates that dexamethasone was present as amorphous form when dispersed in PEG-6000. Thus its aqueous solubility was enhanced upon dispersion in PEG-6000. The blue and green thermograms are identical. If we compare them with pink thermogram, then obviously, there is a dip [though not a sharp peak; as amount of dexamethasone (2 mg) was very less in comparison to the other excipients (648 mg)] at the melting point of dexamethasone. Thus, dexamethasone was in crystalline state when compressed into tablet. Again, the yellow thermogram shows no peak beyond 250 ^{0}C. Thus, it is confirmed that dexamethasone was in amorphous form upon conversion of solid dispersion into tablet; the processing of wet granulation and compression did not affect the solid-state properties of dexamethasone

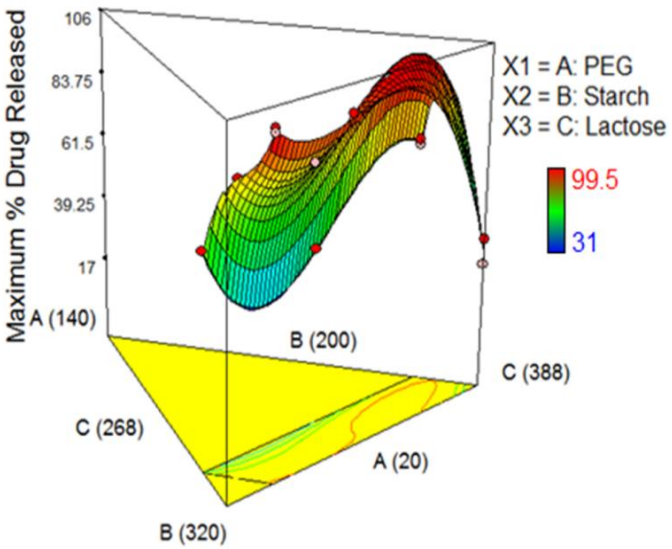

Figure 3. 3D Surface Plot for Maximum % Drug Released. Maximum % Drug Released = -4054.6 * PEG + 17.59 * Starch - 11.74 * Lactose + 10.73 * PEG * Starch + 10.26 * PEG * Lactose -0.015 * Starch * Lactose - 0.013 * PEG * Starch * Lactose + 0.0068 * PEG * Starch * (PEG-Starch) + 0.0057 * PEG * Lactose * (PEG-Lactose)- 0.00015 * Starch * Lactose * (Starch-Lactose).

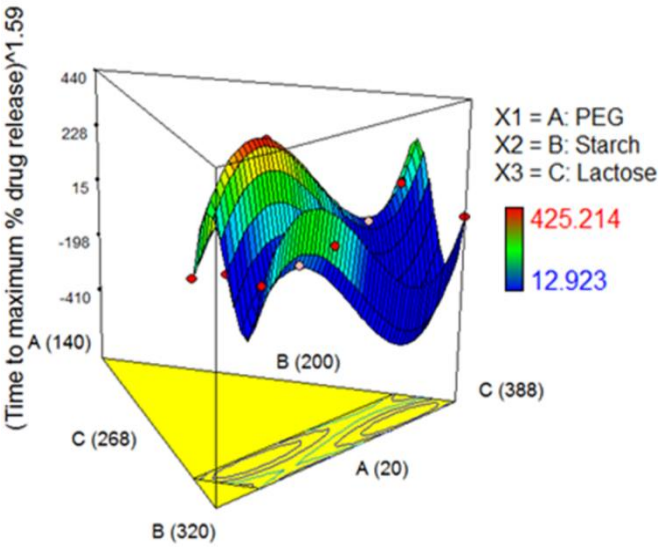

Figure 4. 3D Surface Plot for Time to Maximum % Drug Release. (Time to Maximum % Drug Released) ^ 1.59 = -171872* PEG -296.2 * Starch +127.0 * Lactose + 444.9* PEG * Starch + 446.2 * PEG * Lactose + 0.695 * Starch * Lactose - 0.546 * PEG * Starch * Lactose +0.266 * PEG * Starch * (PEG-Starch) +0.273* PEG * Lactose * (PEG-Lactose) +0.0021 * Starch * Lactose * (Starch-Lactose).

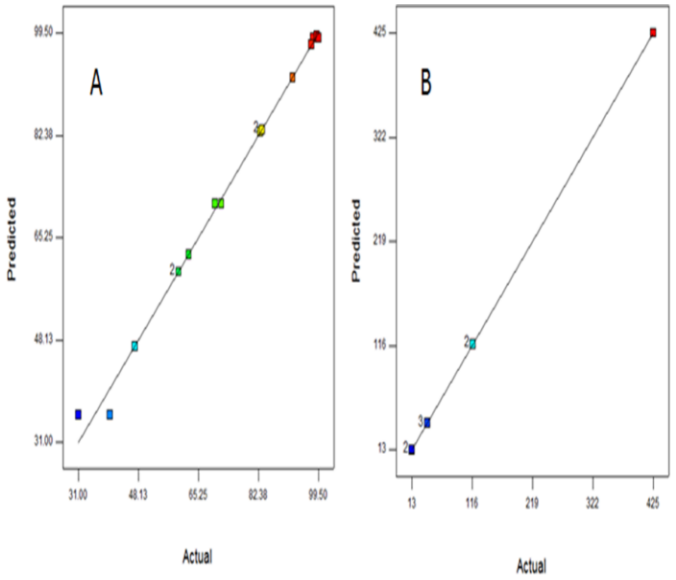

Figure 5. Predicted vs. Actual Plot. A: Maximum % Drug Released. B: Time to Maximum % Drug Released. Presence of the points on/near to diagonal line confirmed the predictability of the developed models in the design space.

Conclusion

Dexamethasone is compatible with PEG-6000. Upon dispersion in PEG-6000, dexamethasone becomes amorphous in nature and also after compression into tablet it remains in amorphous form. Thus, its aqueous solubility is increased leading to faster and complete release from tablet. 16 run Randomized D-Optimal Mixture Design optimized the solid dispersion tablet of dexamethasone that releases 99.5% of drug in 5 minute.

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