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D-Optimal Designing and Optimization of Long Acting Microsphere-Based Injectable Formulation of Aripiprazole

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This work was aimed to design and optimize a long acting microsphere-based injectable formulation of aripiprazole by using D-optimal experimental design methodology. Microspheres were prepared by solvent evaporation method using PLGA and cholesterol as release rate retardant materials. The microspheres were characterized for their encapsulation efficiency, particle size, surface morphology, residual solvent content, and drug release behavior. Contour plots were plotted to study the encapsulation and release behaviour of the drug from the microspheres. Desirability technique was used for the optimization of microsphere formulation composition. By using an optimum blend of drug and cholesterol in the microsphere formulation it was possible to attain a consistent drug release for a period of 14 days. The results have confirmed that the D-optimal experimental design technique can be successfully employed for designing the long acting microsphere dosage form.

Keywords aripiprazole; cholesterol; D-optimal design; microsphere; optimization; PLGA

INTRODUCTION

In the treatment of schizophrenia, atypical antipsychotic drugs are the choice of the physician as these drugs are therapeutically more effective and produce fewer side effects when compared to typical antipsychotic agents. The antipsychotic drug therapy requires continuous administration of the drug for a long period of time, ranging from several months to years. Due to non-compliance of psychotic patients for dosage administration, successful management of the disease is a difficult task (Bhanji & Margolese, 2004). In general, the long acting depot injections of antipsychotic drugs could reduce the frequency of drug administration to the extent of once weekly to once a month and, thus, can considerably improve patient compliance desired in the effective management of the disease (David & Adams, 2001; Gerlech, 1994).

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Aripiprazole, a novel atypical antipsychotic drug, has a unique pharmacologic profile, that is, partial agonist activity at dopamine D-2 receptors, partial agonist activity at serotonin 5-HT1A receptors, and antagonist activity at serotonin 5-HT2A receptors (Grunder et al., 2006; Harrison & Perry, 2004). Presently aripiprazole is commercially available in the form of conventional tablets, oral solution, and intramuscular injection. These products are prescribed with a once a day dosage regimen for several months. Due to psychological problems, daily administration of these products is uncertain as patients may be reluctant to take the medications on their own. Frequent drug missing or interruptions in the drug administration leads to the failure of drug therapy. The aim of the present work was, therefore, to develop a long acting injectable formulation of aripiprazole which would produce continuous and consistent drug delivery for a period of at least two weeks without any involvement on the patient's part in daily dose administration.

The PLGA is extensively used as a polymeric carrier for the formulation of long acting depot injections because of its biocompatibility, predictable biodegradability, ease of formulation, and regulatory approval for parenteral application (Anderson & Shive, 1997; Sinha & Trehan, 2005; Wang, Kleiner, & Venkatraman, 2003). However, PLGA is a very expensive polymer and therefore its high cost limits its application in designing drug delivery systems for treating disease where the therapy is to be continued for years. Cheaper substitutes of PLGA for the designing of microsphere-based drug delivery systems were investigated. Since cholesterol is biocompatible, nontoxic hydrophobic, possesses all the desired qualities of good release rate controlling material, and approved by the FDA for i.v. injectable formulations, it was considered as the ideal substitute for PLGA for the present depot injection development studies.

For the development of microsphere-based long acting formulations, a two-step procedure has been recommended. First, screening study of the release rate controlling carriers is performed; then, further studies on the complete model formulation with the selected carriers, each at a realistic level, is conducted to verify the encapsulation and actual release of the

drug in the final formulation. In this step, the most suitable mixture composition to get the highest drug loading and consistent drug release up to 14 days is identified. Experiments for highest drug loading and optimized release can be set up according to a statistical experimental design. The application of statistical experimental design and optimization studies in the pharmaceutical product development has been demonstrated to be an efficient and satisfactory method to acquire the necessary information that correlates the independent variables, or factors, with the dependent variables, or responses, relevant to formulation composition (Parikh et al., 2003; Uchida, Yoshida, Ninomiya, & Goto, 1995). When the measured responses are assumed to depend only on the proportions of the ingredients present in the mixture, it is possible to use experimental mixture design for optimization studies. A mixture design experiment is a special type of response surface experiment in which the factors are the components of a mixture and the response is a function of the proportions of each ingredient. The mixture components cannot range in an independent way since their sum has to be equal to 100% and specific experimental matrices and mathematical models have to be used. This approach is suitable for the study of the effects of changes in mixture composition and selection of an optimal composition of the microsphere formulation for achieving the prefixed target with the least number of experiments (Mura et al., 2005). D-optimal mixture design is commonly used to reveal main effects and interaction effects between the independent variables of the experiment (El-Malah, Nazzal, & Khanfar, 2006).

The present studies were aimed to develop and characterize long acting microsphere formulation of aripiprazole employing D-optimal mixture design technique of optimization and exploring the possibility of using cholesterol as a substitute of PLGA as a release rate controlling material for designing and developing long acting microsphere-based formulation.

MATERIALS AND METHODS

Materials

Aripiprazole was kindly donated by Torrent Research Center, Ahemdabad, India. Polylactide-co-glycolide 50:50 (Resomer RG 502 H, Mw 41,000, Intrinsic viscosity 0.41 dl/g, Boehringer Ingelheim, USA), Polylactide-co-glycolide 75:25 (Purasorb, Mw 15,000, Intrinsic viscosity 0.14 dl/g, Purac Polymers, Netherland), Polylactide-co-glycolide 85:15 (Purasorb, Mw 20,000, Intrinsic viscosity 0.18 dl/g, Purac Polymers, Netherland), and Polyvinyl alcohol (Mw 88,0000, Nippon chemicals, Japan) were obtained as a gift samples. Sodium alginate, casein, cholesterol, and dichloromethane were purchased from s.d. fine chem., India.

Preparation of Microspheres

Aripiprazole loaded microspheres were prepared by solvent evaporation method (Table 1). Briefly, 100 mg of aripiprazole and 400 mg of release rate retarding carrier were dissolved in 1.5 ml of dichloromethane. The resulting solution was drop wise added under homogenization (Scientech, India) into aqueous phase containing 100 ml of 0.5% polyvinyl alcohol (PVA). The resulting emulsion was stirred for 3 h on a magnetic stirrer for the removal of dichloromethane. The solidified microspheres were recovered by centrifugation (Remi C-24, India) for 10 min at 3000 rpm. The microspheres were washed three times with water to remove traces of PVA. Finally the microspheres were dried by lyophilization (Virtis bench top 2K, USA).

TABLE 1
Optimized Conditions Employed in the Solvent Evaporation Method

S. No.	Variable	Optimized Condition
1	External aqueous phase temperature	10°C
2	Surfactant type and concentration in the external aqueous phase	0.5% PVA
3	Volume of external aqueous phase	200 ml/gm of batch
4	Solvent evaporation time and temperature	3 h at 30°C
5	Drying methodology of the fabricated microspheres	Lyophilization

Experimental Design

Design Expert (version 7.1, Stat-Ease Inc., Minneapolis, USA) software program was used for the experimental design. A 14 run, 4 replicate, D-optimal mixture design was employed in this study to construct polynomial models for the optimization process. This design provides an empirical model to describe the effect of formulation ingredient on the encapsulation efficiency and drug release from the microsphere formulation. Validity of experimental design was confirmed by plotting a standard error of design graph. The probability value (α) for determination of statistical significance was set at 0.05, which indicated that a "hypothesis" theory would be rejected if the calculated *p*-value were less than 0.05 in favor of an alternate theory. Models were selected on the basis of sequential comparison and lack of fit test. Significance of the models was further confirmed by statistical analysis. Response surface, contour plot, and overlay plots were constructed for the response variables.

Encapsulation Efficiency, Loading Capacity and Percentage Yield of Fabricated Aripiprazole Microspheres

The microspheres equivalent to 10 mg aripiprazole were dissolved in minimum quantity of dichloromethane and then

diluted with the mobile phase. The resulting solution was filtered through 0.45 μ filter paper and filtrate was estimated for aripiprazole by RP-HPLC method using Waters HPLC, C-18 BDS (250 × 4.6 mm) column, phosphate buffer (pH 3.0):acetonitrile:methanol (50:25:25) as mobile phase and 1.5 ml/min flow rate at 260 nm. The percent encapsulation efficiency was calculated as: (Actual drug loading/Theoretical drug loading) * 100.

The percent loading capacity of the micropsheres was calculated as: (mg of loaded aripiprazole/mg of microsphere) * 100.

The percent yield of microspheres was calculated as: (Practical yield/Theoretical yield) × 100.

In Vitro Dissolution Study

Microspheres (10 mg) were placed in 10 ml phosphate buffer solution (pH 7.4) containing Tween 80 (0.5% w/v) and sodium azide (0.01%) in 15 ml culture tubes. The culture tubes were incubated in a shaker water bath (Jindal, India) at 37 ± 1ºC. At predetermined time intervals glass tubes were withdrawn and the contents of each tube was centrifuged for 10 min at 2000 rpm. The supernatant was discarded and the residual cake was collected and dissolved in the minimum quantity of dichloromethane and estimated for drug content by HPLC method in the previous section.

Particle Size

Particle size of microspheres was determined by laser diffraction based particle size analyzer (Malvern mastersizer 2000, UK). Microspheres were suspended in a 1% aqueous solution of Tween 80 and sonicated for 60 s prior to particle size determination. Polydispersity was calculated by the following formula: Polydispersity = $(D_{0.9} - D_{0.1}) / D_{0.5}$, where $D_{0.9}$, $D_{0.5}$, and $D_{0.1}$ are the particle diameters determined at the 90^{th}, 50^{th}, and 10^{th} percentile of undersized particles respectively.

Morphology of the Microspheres

The morphology of microspheres was studied by scanning electron microscope (Jeol JSM 6100). Samples were mounted on the metal stubs and sputter coated with gold for 5 min prior to examination under SEM.

Residual Solvent Analysis

The amount of residual solvent (dichloromethane) in the microspheres was analyzed by gas chromatography (Perkin Elmer Autosystem XL with turbomatrix 16). Fabricated microspheres were dissolved in N-methyl pyrrolidione and quantified with a flame ionization detector using capillary DB-624 (30 M × 0.53 mm × 3.0 μ) column (Agilent technology) and nitrogen as a carrier gas. Isothermal conditions were used with injector, oven, and detector temperatures of 160, 200, and 240ºC, respectively. Calculation was based on a standard curve constructed with known dilutions of dichloromethane.

RESULTS AND DISCUSSION

The primary objective of the present work was to design and develop long acting microsphere-based injectable formulation of aripiprazole. Microspheres were fabricated by solvent evaporation method. The formulation variables for the fabrication of microspheres by the solvent evaporation method were fixed as shown in Table 1. In the pre-optimization studies PLGA 50:50, PLGA 75:25, PLGA 85:15, cholesterol, sodium alginate, and casein were used as release rate retarding material for the fabrication of microspheres and a 20% w/w drug was loaded in the microspheres. Drug encapsulation efficiency of the sodium alginate and casein microspheres was 40.5 and 29.2%, respectively. The reason for the poor encapsulation efficiency with the sodium alginate and casein may be due to the poor drug retaining ability of these materials. On the other hand, the encapsulation efficiency of microspheres of the remaining four carriers, cholesterol, PLGA 50:50, PLGA 75:25, and PLGA 85:15 (Batch no.: Ari-chol, Ari PLGA 50:50, Ari-PLGA 75:25, and Ari-PLGA 85:15) were found to be 91.28, 87.29, 78.12, and 75.12%, respectively and during release study the r^2 value of these microspheres were found to be 0.8812, 0.8771, 0.8226, and 0.8575, respectively. On the basis of better results of the encapsulation efficiency and drug release study (Figure 1) the cholesterol and PLGA 50:50 were selected for the final optimization studies.

To know the optimum mixture of aripiprazole, PLGA 50:50, and cholesterol for the formulation of microspheres, pre-optimization study levels of each variable and their combinations were defined (Table 2). The D-optimal mixture design, which is a powerful tool for the optimization of formulations of mixtures when limitations and restrictions regarding the

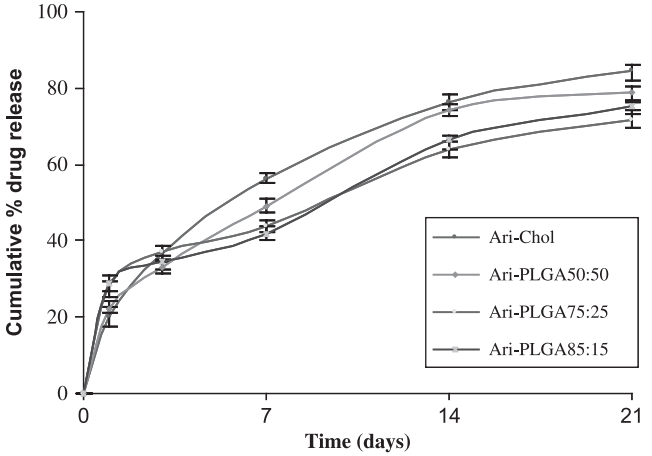


FIGURE 1. Cumulative drug release from aripiprazole microspheres (pre-optimization study).

TABLE 2
Restrictions of Component Proportions in the Experimental Design

Design Constraint	High Level	Low Level
A (% of Aripiprazole)	30	10
B (% of PLGA 50:50)	90	0
C (% of Cholesterol)	90	0
A+C =	100	10
B+C =	90	70
A+B =	100	10
A+B+C =	100	—

experimental designs are more, was selected for the optimization of microsphere dosage form. This technique need fewer number of optimization trials as compared to other optimization techniques. Fourteen experiments were designed and then experimentally performed for the optimization of microsphere composition (Table 3). Three independent variables, aripiprazole, PLGA 50:50, and cholesterol, and five response variables, encapsulation efficiency and drug release (1, 3, 7, and 14 days) were selected for the final optimization studies. The standard error of design was less than 1 in the entire design space, which confirmed that the designed experiments were statistically significant.

The primary five responses, that is, encapsulation efficiency (R_1) and drug release at 1, 3, 7, and 14 days (R_2, R_3, R_4, and R_5), were analyzed by using the Design-Expert software. The first step towards an optimal statistical analysis was to select the model that best describes and fits the obtained data. Therefore, results were first analyzed by the sequential model comparison and lack of fit test. Based on the results of the sequential model comparison (Table 4) the cubic, quadratic, special cubic, linear, and special cubic models were, respectively, selected for the response variables (R_1 to R_5). Sequential model comparison test showed the statistical significance of adding the model terms in the already existing model. The lack of fit test was subsequently performed to further demonstrate the suitability of the fitting of the selected model. Lack of fit test was calculated based on the residual sum of square, diagnosed suitability of the models for data fitting. As shown in Table 4, large *p*-values show insignificant lack of fit test, which further confirms that the selected models adequately fit the data. Table 5 enlists other statistical data of the selected models of all five response variables. The adjusted R- squared and predicted R-squared values did not have a difference greater than 0.2; this also confirmed that the models were statistically significant and suitable to fit the data.

The following polynomial equations were constructed and used to demonstrate the relationship between the formulation ingredient – Aripiprazole (A), PLGA 50:50 (B), Cholesterol (C), and the response R_1 to R_5.

$$\begin{aligned}\text{Encapsulation efficiency } (R_1) = {} & -1127.20*A + 92.65*B \\ & + 94.8*C + 1641.18*AB + 1923.70*A*C \\ & + 389.20*A*B*(A-B) + 731.23*A*C*(A-C) \\ & - 9.96*B*C - 1105.51*A*B*C \\ & + 10.33*B*C*(B-C) \end{aligned} \quad (1)$$

TABLE 3
14 Run D-Optimal Experimental Plan for the Optimization of Aripiprazole Microsphere

	Independent Variable			Response Variable				
Run	A(% of Aripiprazole)	B (% of PLGA 50:50)	C (% of Cholesterol)	R_1 (% Encapsulation Efficiency)	R_2 (% Drug Release 1 Day)	R_3 (% Drug Release 3 Day)	R_4 (% Drug Release 7 Day)	R_5 (% Drug Release 14 Day)
1	20	80	0	89.3	19.4	34.3	52.2	78.2
2	30	0	70	84.3	22.9	38.4	58.7	81.3
3	10	0	90	95.2	17.9	32.6	52.4	78.4
4	10	0	90	94.4	17.0	33.6	51.3	73.7
5	10	90	0	93.1	18.2	31.3	49.4	74.4
6	30	70	0	67.6	26.9	39.1	54.3	74.4
7	10	90	0	92.2	18.7	29.5	49.3	74.3
8	15	20	65	91.2	19.1	41.2	51.2	71.4
9	30	0	70	86.7	23.1	42.4	59.3	82.7
10	15	65	20	92.4	20.4	43.7	57.4	76.1
11	30	70	0	68.1	27.6	49.3	59.1	78.1
12	10	45	45	91.2	18.1	41.4	51.9	69.2
13	20	0	80	92.8	17.0	39.1	54.3	79.3
14	30	35	35	75.7	24.3	29.5	58.7	84.7

TABLE 4
Statistical Model Comparision and the Corresponing Lack of Fit Test

	Sequential Comparision					Lack of Fit				
	p-Value					*p*-Value				
Type of model	R_1	R_2	R_3	R_4	R_5	R_1	R_2	R_3	R_4	R_5
Linear	0.0003	0.0001	0.4363	0.0008	0.0174	0.0016	0.073	0.1502	0.3246	0.1503
Quadratic	0.0007	0.0118	0.6531	0.6885	0.5465	0.0351	0.0368	0.0965	0.2204	0.1093
Special cubic	0.8744	0.5782	0.0127	0.9864	0.0271	0.0230	0.0268	0.3750	0.1541	0.2959
Cubic	0.0230	0.0263	0.3750	0.1541	0.2959	0.0431	0.0564	0.0312	0.3210	0.3650

TABLE 5
Summary Statistics for the Response Variables

Response Variable	Model	*F* Value	Df	*p*-Value Prob > *F*	*R*-Squared	Adjusted *R*-Squared	Predicted *R*-Squared
R_1	Cubic	10.48	3	0.0230	0.9967	0.9892	0.9253
R_2	Quadratic	7.16	3	0.0118	0.9555	0.9278	0.8694
R_3	Special cubic	11.36	3	0.0127	0.7245	0.5882	0.5123
R_4	Linear	14.74	7	0.0008	0.7282	0.6788	0.6037
R_5	Special cubic	5.44	6	0.0271	0.8233	0.6719	0.5267

Df: Degree of freedom.

$$\text{Release at 1 day } (R_2) = 194.33 *A + 18.45*B + 17.47*C - 177.40*A*B - 197.09*A* + 4.05* B* C \quad (2)$$

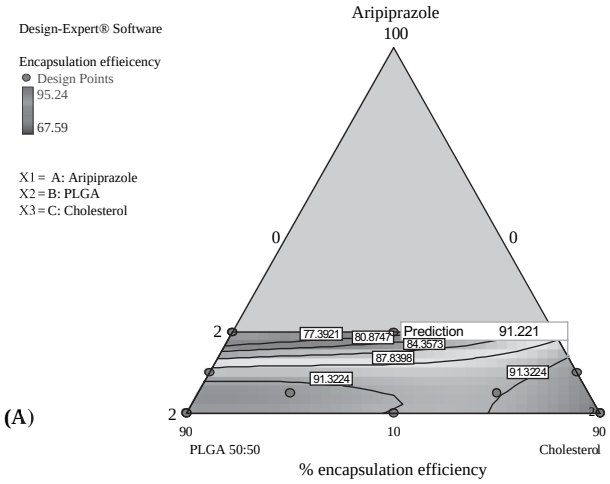
$$\text{Release at 3 day } (R_3) = -75.14 *A + 29.97*B + 33.18*C + 210.78 *A*B + 80.89 *A*C + 51.32*B*C - 545.34*A*B*C \quad (3)$$

$$\text{Release at 7 day } (R_4) = +81.98 *A + 50.19 *B + 51.92 *C \quad (4)$$

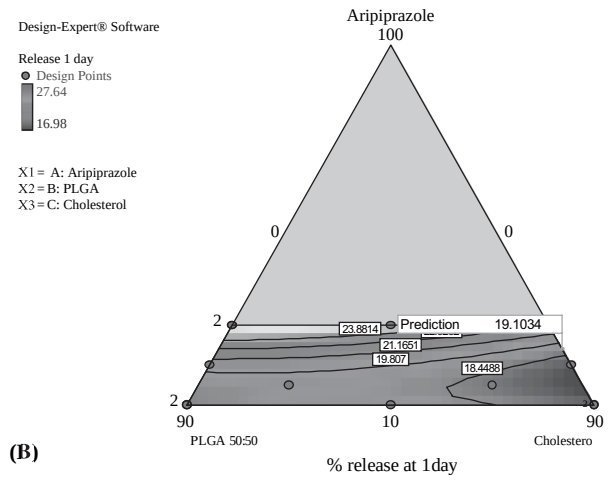
$$\text{Release at 14 day } (R_5) = + 47.27 *A + 75.11* B + 75.37*C + 46.28*A*B + 72.95*A*C - 27.99 *B*C + 268.96 *A*B* C \quad (5)$$

Normal plot of residual, residual vs. predicted, and predicted vs. actual graph of all the response variables confirmed that there was no need for data transformation for further analysis as the data were statistically significant for the prediction of the desired optimum microsphere composition.

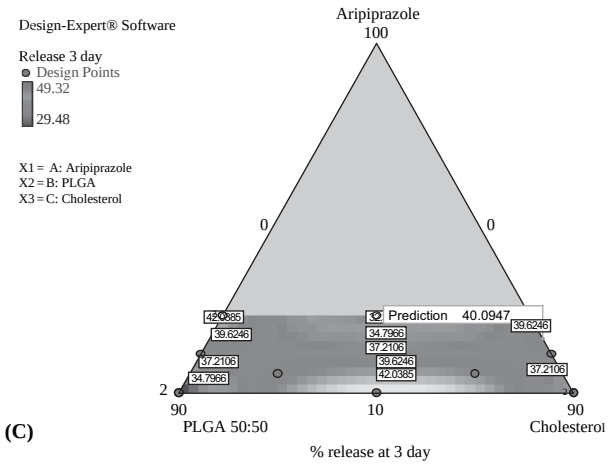
Optimization of formulation variable was done by fitting desired release objectives in the designed model. The effect of formulation ingredients on the response R_1 is schematically presented in Figure 2 (A) as a two dimensional contour plot. This can be used to extrapolate data about the percentage of drug encapsulation at any given concentraion of the ingredients within the limits of the experimental design. The contour plot showed that with increasing the composition of drug in the microsphere formulation drug encapsulation capacity was decreased. This could be attributed to the limited loading capacity of the encapsulating carriers, that is, cholesterol and PLGA. As the ratio of the drug in the formulation increases, the amount of the drug that was not encapsulated remains in the free form and, thus, results in low encapsulation efficiency of the formulation. The effect of formulation ingredients on the drug release (R_2–R_5) is shown in Figure 2 (B–E) as a two dimensional contour plot. Figure 2 (B) shows that initial burst drug release (day 1) from the microsphere was dependent on the ratio of drug and release controlling carrier, that is, cholesterol and PLGA. Cholesterol and PLGA both have a significant positive effect on the drug release and contour plot



(A)



(B)



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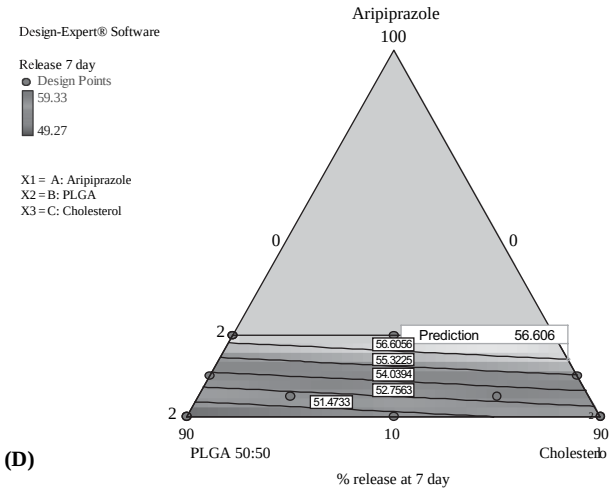
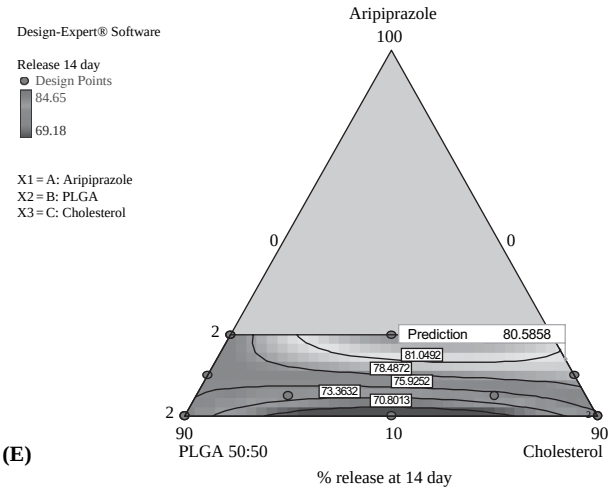


(D)



(E)

FIGURE 2. Contour plot showing the effect of formulation variables and prediction of optimum response of (A) encapsulation efficiency, (B) drug release at 1 day, (C) drug release at 3 days, (D) drug release at 7 days, and (E) drug release at 14 days.

showed that the initial burst release (day 1) was less when the amount of cholesterol was increased in the formulation as compared to the PLGA polymer. This suggests that the cholesterol is having more drug loading capacity as compared to the PLGA polymer. Contour plot for the drug release at day 3, 7, and 14 also were constructed as shown in Figure 2 (C, D, and E), which further confirmed that the drug release from the cholesterol was better controlled as compared to the PLGA. Figure 2(E) further reveals the drug release from the formulation at day 14 was more with cholesterol as compared to the PLGA containing formulation. For the optimization of formulation composition, desirability technique was used. The desirable objectives were (a) the ratio of drug should be maximum, (b) the encapsulation efficiency should be maximum, (c) the drug release at day 1 should be less, and (d) drug release at day 14 should be maximum. Based on the desired critera, three optimized solutions were predicted by the software and the solution that had more desirability value (0.779) was selected as an optimized formulation. The predicted optimized microsphere contained 24.029% aripiprazole and 75.971% cholesterol. The predicted optimized microspheres were prepared and evaluated. The drug release profile of the predicted and fabricated optimized microspheres is shown in Figure 3. The r-value of observed and predicted formulation batch was found to be 0.9566 and 0.9502, respectively. Further, a graph was plotted between the observed and predicted drug release, and observed and residual drug release (Figure 4 A, B); this showed that the observed and predicted responses were in close agreement with each other. The drug release profile also showed that the designed microspheres were capable of releasing the drug for 14 days. Interestingly, the cholesterol-based microspheres had shown better drug encapsulation and drug release controlling potential as compared to the PLGA based microspheres.

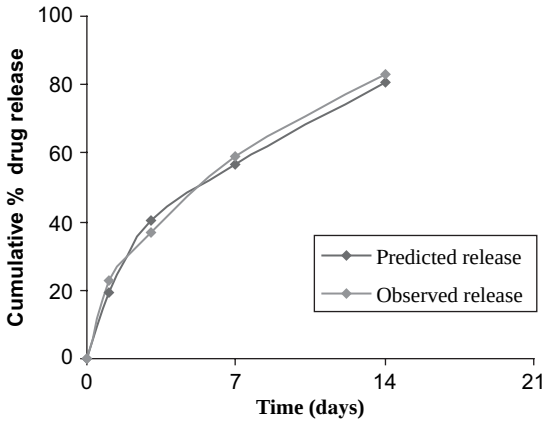


FIGURE 3. Predicted and observed drug release from the optimized aripiprazole micropshere formulation of aripiprazole micropshere.

Drug Encapsulation, Loading Capacity and Yield

The D-optimal designing result predicted that the encapsulation efficiency of the optimized cholesterol microspheres will be 91.21% with respect to 24.029% drug loading. When it was experimentally confirmed it was found that at 21.91% drug loading, the drug encapsulation efficiency was 96.12%, which was in close agreement with the predicted value. The drug loading capacity of the cholesterol microsphere was 21.05%. The yield of the microspheres was found to be dependent on the size of the batch. On increasing the batch size of microsphere formulation from 1 gm to 5 gm the yield was increased from 72.25% to 82.18%.

Drug Release Mechanism

The drug release data of the optimized aripiprazole cholesterol micropsheres were analyzed on the basis of Korsmeyer-Peppas equation and Higuchi kinetics. Coefficient of correlation (r) was used to evaluate the accuracy of the fit. Data of the optimized microsphere formulation was treated by Higuchi equation (r = 0.9997) and Korsmeyer-Peppas equation (r = 0.998, n = 0.43). This data treatment showed that the drug release pattern followed a fickian type behaviour, which shows that the drug release from the microsphere was controlled by the diffusion mechanism.

Residual Solvent Analysis

As per ICH Q 3 (C) guideline the maximum limit for the residual dichloromethane (DCM) in a product is 600 ppm. In the optimized fabricated aripiprazole loaded cholesterol microsphere, the content of DCM was found to be 210 ppm which was well below the above prescribed limit.

Particle Size Analysis

In the particle size analysis of the optimized microsphere, the values of $D_{0.1}$, $D_{0.5}$, $D_{0.9}$, and polydispersity were found to be 4.36, 17.20, 39.22, and 2.02, respectively. The maximum particle size of the microspheres was below 60 μm. The above particle size distribution of the microspheres can be considered well acceptable for intramuscular administration.

Surface Morphology and Characteristics

Figure 5 shows the morphological characteristics of optimized microsphere. The SEM photomicrographs of the microspheres reveal that they are spherical, nonporous, and uniform particles with a smooth surface.

SUMMARY AND CONCLUSION

An attempt was made to fabricate microsphere-based long acting injectable formulation of aripiprazole with the help of D-optimal statistical optimization technique. The release of drug from the microspheres demonstrates the feasibility of

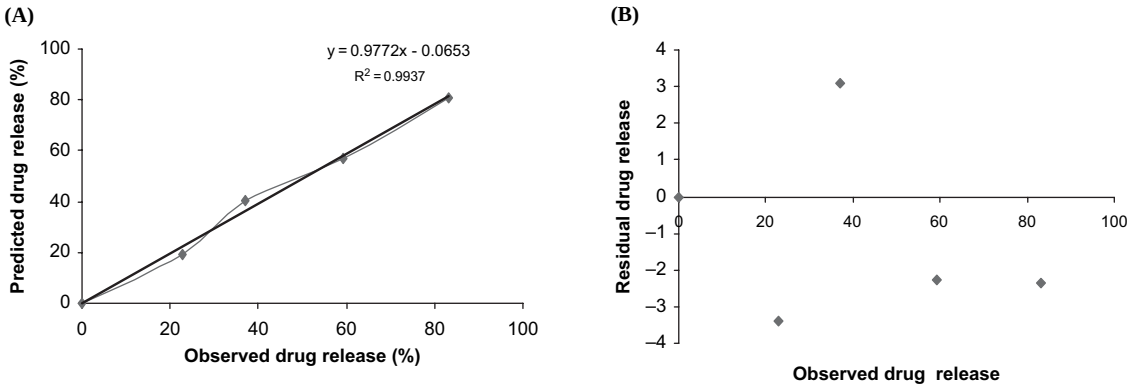


FIGURE 4. Linear and residual plots between observed and predicted values of drug release of the aripiprazole microsphere at 1, 3, 7, and 14 days.

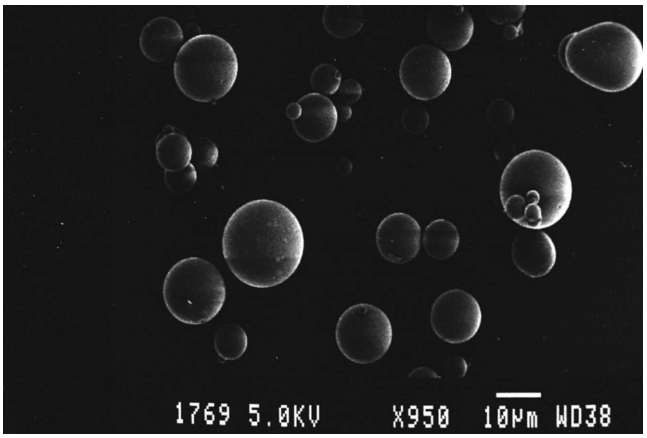


FIGURE 5. SEM photograph of the optimized aripiprazole cholesterol microsphere.

designing a system of aripiprazole using cholesterol as release retarding material for staged release up to 14 days. The results support the substitution of PLGA by cholesterol in designing a long acting parenteral controlled release formulation.

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