RESEARCH ARTICLE

Comparison Study of Aloin-Curcumin Nanoparticles by Taking 2 Different Ratios and Analyses by Using Drug Design Experimental Study

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ABSTRACT

Numerous chemopreventive drugs like aloin and curcumin have demonstrated potential effects in cancer treatment; however, their efficacy is limited by low bioavailability. Thus, the primary goal of this research was to formulate a unique method by using the herbal drugs synergistically and improve the bioavailability of these anticancer drugs here, using the nanoprecipitation method for two well-active constituents of known natural herbal compounds. Aloin (AL)-curcumin (CUR) were co-loaded into polymeric nanoparticles made of poly (D, L-lactide-co-glycolide) and surfactant-polyvinyl alcohol, with the experiment's response being evaluated using Stat-Ease software. To create dual-loaded nanoparticles containing aloin and curcumin, using different ratios sand optimizing the best formulation. (60:120). For aloin curcumin, optimize the better formulation with controlled release formulation having less than 100 nm size of particle and drug entrapment was 86.09% while for (60:60) of aloin -curcumin having 99.1 nm particle size of drug and encapsulation efficiency was 72.05%.

Keywords: Nanoparticulate, Design expert, Phytochemicals, Controlled release, Aloin- curcumin combination, Radiometric delivery.

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INTRODUCTION

Enhancing hydrophobic bioactive chemicals' potency by nanobiotechnology has been shown to be a promising strategy.[1] Herbal extracts include physiologically active components; however, their bioavailability and effectiveness are diminished due to inadequate absorption. To overcome these limitations, herbal drugs, and nanotechnology merging are the best ways.[2] The delivery of medications has undergone a paradigm change as a result of recent developments in herbal-based technologies that increase drug bioavailability. To improve the bioavailability of many herbal medications and use plant constituents, extracts, and poorly soluble compounds, even in beings these disadvantages of phytochemicals by combinations of nanoform of such forms of drugs can promote the health, clinics, trials sectors.

Clinical research shows that when two or more medications are administered at the same time or on the same day, the combination provides a better response rate than a single agent. This is why drug combination regimens are commonly employed in the clinic to improve therapeutic activity and be helpful in cancer treatments. Synergistic medication combinations may now be co-loaded onto nanoparticles by formulation to obtain increased anticancer effects. Well-designed nanoparticles can change the PK and safety profiles of the free pharmaceutical combination and also allow the accumulation of drugs in cancer[3] and release the medications at a synchronized rate and absorption. Various drugs are combined to increase absorption and their positive outcomes prompted researchers to look more closely at the underlying processes that support the AL-CUR formulation's improved *in-vivo* performance. We postulated that to get much better therapeutic results, synchronization of AL-CUR release and topographical co-delivery of both pharmaceuticals are important. To ascertain the biodistribution of the nanocarrier

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that will formulations and *in-vitro* research of the drugs in different situations, we created this study to establish a connection between physiological modifications to drug formulations and the body's reaction to drug formulations.

Aloin is a P-glycoprotein efflux[4,5] due to this drug being pumped back and mainly one of the disadvantages or, we say, reasons for poor bioavailability where the drug curcumin functions as a P-glycoprotein inhibitor.[6,7] Additionally, cur prevents the transfer of chemotherapy medications from inside cancer cells and diminishes the amount of P-glycoprotein (P-gp), an efflux protein, in colon epithelial cells, as Sagnou reports. The antitumor activity of AL-cur in combination drugs may be improved by blocking P-gp efflux and enhancing drug accumulation in cancer cells.

Particular emphasis on using polymeric nanoparticles PLGA is necessary because of their excellent stability in biological fluids, biocompatibility, lack of toxicity, reduced dose needs, and capacity to degrade naturally over time. It is a colloidal pharmaceutical carrier method used for controlled delivery of medicines that have been conceded FDA approval in the USA and have a high drug delivery rate.[8] By embedding several chemotherapeutic cancer drugs within the framework of polymers, it can frequently be used to make nano formulation which thus allows for prolonged drug release.[9] Typically, both drugs are loaded into heart shells, which are then used for drug delivery in cancer antioxidant,[10,11] and drug bioavailability to increase the bioavailability,[12] the goal of the present work is to create an efficient dual drug delivery (DD)system mediated by PLGA nanoparticles utilizing the nanoprecipitation approach**.**

Materials and Methods

Materials and procedure of drug

- *Apparatus and instrument*

By using a UV-visible spectrophotometer, model: - Shimadzu-1800, balance, measuring cylinder, magnetic stirrer, and sonicator.

- *Materials and reagents*

The use of analytical-grade chemicals and Methanol, Aloin, buffer 7.4 PLGA, curcumin, and PVA.

The procedure of AL-CUR NP

Preparation of Nanoparticles: aloin-curcumin Nanoparticle (AL-CURNP) (60:60) and aloin-curcumin Nanoparticle (AL-CURNP) (60:120)

PLGA polymeric AL-CUR loaded nano formulations were formulated at room temperature the nanoparticle by employing the nanoprecipitation process.[12] Drug (Aloin: Curcumin) by taking in ratio 60:60 and (60:120), Polyvinyl alcohol, a surfactant, and PLGA as polymer were added to both the formulations, and it was continually stirred. The process parameters of both methods, including the polymer concentration and stabilizer concentration, were optimized using Box Behnken designs (BBD).[13] Particle size and entrapment effectiveness were evaluated as two resultant variables for both al-cur drug content evaluated.

Experimental Design

The drug AL-CUR design with one of the methods of the response surface, i.e., BBD design. This design was used to optimize the various parameters for preparing in different ratios of aloin-curcumin (60:60) and (60:120) drug PLGA-loaded nano formulation. The various constraints involved in the formulation of nano were categorized as 3 dependent factors and 2 independent variables, taking 5 central points.[13] The surface methodology of the research was employed to optimize the design of the experiment by using the nanoprecipitation technique. An optimized design created 17 different formulas, including center points and axial points.[14] These formulations were analyzed using encapsulation and nanosized data from different AL-CUR ratios. The drug ratio (60:60) and (60:120), taking the same variables of polymer (A), and surfactant (B), as well as stirring time (C), had a substantial influence on the particle size of both ratio al-cur (Y1, Y2) and entrapment efficiency value (E1, E2) of the formed Np ratios.[15] By taking these three (ABC) variables varying three levels low (1), high (+1), and medium (0).[16,17] A 17 tests were done to help evaluate the factors like the size of the al-cur particle and particle entangle and calculate the results on BBD Design- the software was discussed below in Table 1 (trial Version (vs)13.0.12.0) Stat Ease made in USA).

DoE

The Box-Behnken statistical design investigation was used because, in comparison to other strategies,[18] it required a noticeably fewer number of designed experiments, as shown in Table 2.

Each variable was coded at the levels that matched the first findings of the investigation.[19] The dependent variables of particle size and EE were used to characterize the 17 experimental points created by this strategy (entrapment efficiency). The following model was used to analyze how variables and responses related to each other:

$$Y = \beta_0+\beta_1X_1+\beta_2X_2+\beta_3X_3+\beta_{12}X_1X_2+\beta_{13}X_1X_3+\beta_{23}X_2X_3+\beta_{11}X_1^2+\beta_{22}X_2^2+\beta_{33}X_3^2$$

Table 1: Data elaboration for both dependent variables and independent variables

Drug			*ALOIN: CURCUMIN (60:60) (60:120 mg)*		
Independent factors/variables Low (-1) Intermediate (0)			Real and coded values High (+1)		
Polymer	X_1	(mg)	50	100	150
Surfactant	X_2	(%)	1	2	3
Stirring time	X_3	(min)	10	100	150
Name of the dependent factor			Constraints		
Y_1, Y_2Particle size			Size NM (40-366) and (81-458)		
E_1, E_2Entrapment efficiency (%)			EE % (70-95) (60-100)		

*Here Y1, E1 is for (60:60) and Y2, E2 is for (60:120)

Table 2: Different formulations of aloin curcumin nanoparticles (60:60) (60:120)

	Exp.	*Polymer*	*Surfactant (Factor 2)*	*Stirring time (Factor 3)*	*P.S (60:60)*	*P.S (60:120)*	*E.E (60:60)*	*E.E (60:120)*
Std	*Run*	*A:X1*	*B:X2*	*C:X3*	*Y1*	*Y2*	*E1*	*E2*
		Mg	*%*	*Minutes*	*nm*	*Nm*	*%*	*%*
6	1	1.000	0.000	-1.000	457.8	365.4	84.37	81.21
7	2	-1.000	0.000	1.000	106.8	53.6	77.61	78.5
11	3	0.000	-1.000	1.000	96.1	59.3	81.63	87.8
15	4	0.000	0.000	0.000	148.7	111.2	83.96	86.87
9	5	0.000	-1.000	-1.000	321.6	298.2	79.21	78.64
2	6	1.000	-1.000	0.000	195	198	87.49	81.07
12	7	0.000	1.000	1.000	81.3	42.8	91.05	90.44
1	8	-1.000	-1.000	0.000	113	106.8	77.61	77.23
14	9	0.000	0.000	0.000	156.5	113.6	87.52	89.72
13	10	0.000	0.000	0.000	143.6	113.6	83.39	89.72
17	11	0.000	0.000	0.000	147.8	113.3	84.56	85
3	12	-1.000	1.000	0.000	115.2	88.8	83.35	90.18
16	13	0.000	0.000	0.000	146	115.2	85.89	90.12
10	14	0.000	1.000	-1.000	365.3	256	85.12	94.63
8	15	1.000	0.000	1.000	111.1	75.5	89.12	81.95
5	16	-1.000	0.000	-1.000	251.9	215.3	71.6	75.23
4	17	1.000	1.000	0.000	202.7	167.3	94.4	94.42

*P. S = particle size, E. E = entrapment efficiency

Here Y represents the observed variable response for each variable combination of component levels; β0 is an intercept; β1, β2, and β3 are linear regression coefficients; X_1, X_2, and X_3 are the factors under study; X_{12}, X_{22}, and X_{32} are polynomial quadratic.[20] An analysis of variance, also known as ANOVA, was used to figure out the optimal conditions.

Characterization

Determination of aloin-curcumin (60:60) and (60:120)-entrapment

The percentage of aloin-curcumin (60:60) and (60:120) drug in the produced nanoparticles NP compared to the original quantity of aloin drug employed to produce the nanoparticles is known as drug entrapment efficiency (E.E.) measure in percentage (%).[21] The following equation was used in conjunction with the UV spectroscopy stated above to determine this calculation (Eq. 2).

E.E % = amount of drug in nanoparticle/Initial amount of drug*100

In-vitro study of AL-CUR different ratios of release profile

Examine the *in-vitro* drug AL-CUR release of both ratios' formulations for aloin-curcumin-loaded nanoparticles 60:60 mg and 60:120 mg. For taking both formulations of different ratios apply the same method (dialysis bag diffusion) of drug release. Firstly, phosphate buffer (pH 7.4) in a beaker was utilized for storage of the drug nano formulation within dialysis bags. The beaker was positioned magnetic stirrer, ensuring the temperature of the experiment at 37 °C maintained throughout the experiment, also, the speed was adjusted to 100 rpm.[22,23] At a predetermined time, samples were taken at the same time a new freshly prepared buffer solution was added. Dilutions were analyzed with a UV-visible spectrophotometer at a specific wavelength of nm for both ratios. To elucidate the kinetics data and interpret the *in-vitro* drug data.

Kinetics study of both drugs

The zero-order rate equation is applicable for characterizing systems where the concentration of the drug does not affect the rate of release.

Cumulative% drug released vs time = zero (0) order kinetic model

In contrast, the first-order equation is relevant for scenarios where the release rate is concentration-dependent.

The time-dependent logarithm of the cumulative percent of drug =. First (1st) order kinetic model

Higuchi's model suggests that the release of drugs from an insoluble matrix is controlled by Fickian diffusion and proportion to the square root of time.

Table 3: Elaborate data of both formulations taking different ratio

Source	*Particle size (60:60)*	*Particle size (60:120)*	*Entrapment efficiency (60:60)*	*Entrapment efficiency (60:120)*
Model suggestion	Significant	Significant	Significant	Significant
Lack of fit	Non-significant	Non-significant	Not significant	Not significant
Standard deviation	7.43	1.75	1.41	2.0
C. V.%	4.00	1.19	1.68	2.34
Mean	185.9	146.7	83.99	85.45

Cumulative %percentage of release of drug behavior against the square root of time =. Model by Higuchi, Different techniques were utilized to characterize the *in-vitro* release profile.[24] According to the regression coefficient, the value of the model the best model was chosen.[25]

RESULTS AND DISCUSSION

Preparation of Nanoparticles aloin-curcumin (60:60) and (60:120)

The synthesis of nanoparticles drug aloin-curcumin (60:60) and (60:120) using the nanoprecipitation approach is an efficient technology since it produces nanoparticles easily and makes scaling up the manufacturing process relatively possible. The optimal Al-CUR concentration in different ratios, PLGA, stirring duration, and PVA were obtained by optimizing the crucial formulation factors that affected the NPs' production. The impacts of the independent factors (X1–X3) on the dependent variables (Y1–Y2) were examined using the BBD design as a tool for both ratios.[26-38]

Drug AL-CUR particle size effect of both ratios 60:60 and 60:120 (Y1 and Y2)

The regression equation below illustrates how the responses to the particle size (Y1, Y2) influence are

$$Y1 = 175.28 + 1.13X_1 + 35.12X_2 - 2.98X_3 + 0.027X_1X_2 - 0.018X_1X_3 - 0.26459X_2X_3 + 0.0045X_1^2 - 3.93X_2^2 + 0.023X_3^2 \quad \text{.....Eq. 1}$$

$$Y2 = 113.38 + 42.71X_1 - 13.42X_2 - 112.9X_3 - 3.17X_1X_2 - 32.055X_1X_3 - 6.42X_2X_3 + 20.10X_1^2 - 6.73X_2^2 + 43.96X_3^2 \ldots\ldots\ldots\ldots\ldots\ldots\text{Eq. 2}$$

The R2 value in the model for 60:60 Y1 was 0.9729 and Y2 0.9998, while the (actual) addressed R2 value of 60:60 0.9950 and 60:120 model was 0.9996. The crucial model terms of formulation 1 (60:60) that affect the size of the nanoparticles are A, A², AC, BC, C, C², are significant model terms and formulation 2 (60:120) A, A², AB, AC, B, B², BC, C, and C². 23.62% chance of noise happening in a value that fits into the F-value. The data suggests a good non-significant value of lack of fit; thus, a negligible lack of fit is acceptable.

The adequacy of both formulations in the quadratic model is further demonstrated by the fact that the actual R2 value was greater than the adjusted R2 value (0.9950,0.9996). In Eq. 1, the polynomial Eq. (equation) 1 and 2 between the explanatory variables and the particle of drug size are displayed in Figures 1 and 2.

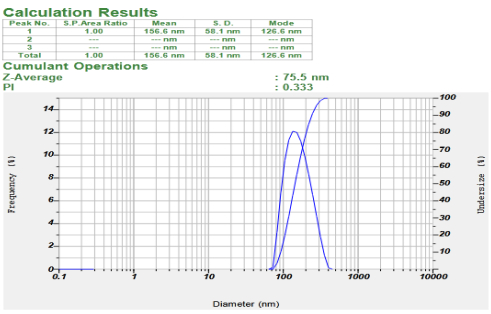

Figure 1: Particle size AL-CUR data of ratio of 60:120 mg

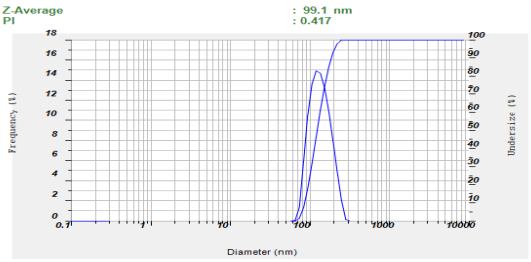

Figure 2: Particle size data of AL-CUR ratio of 60:60 mg

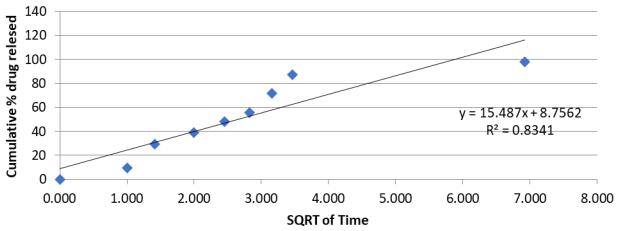

Figure 3: Shows of Higuchi model for 60:60 mg

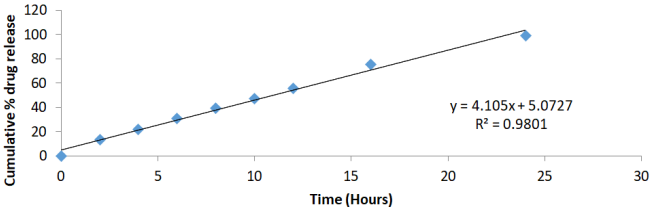

Figure 4: Zero order 60:120 mg AL-CUR

Table 4: *In-vitro* profile of drug different ratios of AL-CUR

Formulation (60:60)				
Kinetic-models	*Zero Order Kinetic*	*First Order Kinetic*	*Higuchi*	*Korsmeyer-Peppas*
Kinetic- Value	$R^2 = 0.573$	$R^2 = 0.772$	$R^2 = 0.834$	$R^2 = 0.660$
Formulation (60:120)				
Kinetic value	$R^2 = 0.9801$	R^2=0.5859	$R^2 = 0.9379$	$R^2 = 0.8775$

Table 5: Drug = Aloin:Curcumin (60:120 mg and 60:120 mg)

S. No.	*Values*	*Polymer (mg)*	*Surfactant (%)*	*Time (min.)*	*Size (nm)*	*E.E (%)*
60:60	Actual value	75.4	1.0	112	99.1	72.05
60:60	Predicated value	75.4	1.0	112	99.5	79.9
60:120	Actual value	80.2	1.2	86.5	75.5	86.89
60:120	Predicated value	80.2	1.2	86.5	77.5	85.08

Drug AL-CUR entrapment efficiency of both ratios 60:60 and 60:120 (E1 AND E2) effect

The regression equation below illustrates how the responses to the entrapment efficiency (E1, E2) influence are

$$E1 = 85.06+5.65\ X_1+3.5X_2+2.388\ X_3+0.29X_1X2-0.31X_1X_3+0.87\ X_2X_3-1.462\ X_1^2+2.1X_2^2\ -2.91X_3^2 \text{.....Eq. 3}$$

$$E2 = 82.28+2.19X_1\ -5.62X_2\ +1.12X_3\ +0.10X_1X_2-0.63X_1X_3-3.33X_2X_3\ -5.60X_1^2-3.04X_2^2+3.45X_3^2\ \text{.....Eq. 4}$$

The ANOVA result for EE is shown in Table 3 after the experiment's analysis. Model terms qualify as significant when their *p-values* are 0.69988.

The experiment's F-value was 0.36 and 15.17, which suggests a good fit for the model. A, B, C, B^2, and C^2 are significant model terms in the case of 60:60, and in the case of 60:120A terms, B terms, BC terms, A2 terms, B2 terms, and C2 terms are qualified important model terms in this instance. In both experiments, models were to fit—a non-significant lack of fit.

The model's R2 value, which was 0.9333 in the first experiment and in the second experiment it comes to 0.9529, was come to be higher than the changed R2 value, which was 0.8641 and 0.9176. It provides significant support for the present quadratic model's fit. The drug's aloin and curcumin different ratio composition was shown to have a beneficial impact by the positive sign of before the coefficient of X. In a similar layer, the positive sign before the coefficient of X2 suggested that PLGA improved the drug's effectiveness in NP encapsulation.

***In-vitro* Profile of AL-CUR Drug Release**

Drug release of both ratios of drug AL-CURnp was analyzed properly as per the guidelines the temp. (37°C), conditions like buffer pH 7.4 maintain the same in both experiments. The figure of AL-CUR release behavior is shown with the help of graphs and tables shown in Figures 3, 4, and Tables 4 & 5 observation indicating the release of AL-CUR depends on the loading entrapment as well as the composition of the nanosized particle.

Optimization and Observation by Software

The Design-software-program trail *vs* 13.0.0.1 recommended the optimal processing settings for AL-CUR-loaded PLGA 60:120 nanoparticles with 1.00 desirability. With an optimized PVA content of 1.0 and 1.2%, an optimal PLGA concentration of 75.4 and 80.2 mg, and a stirring rate of 112 and 86.5 minutes, observed in the predicted formulation was evaluated by software. Particle size (P.S) was taken nm, and both ratios of drug AL-CUR efficiency (%), were measured after the formulation was produced. A relative error was computed by comparing the experimental values of the replies with the expected values derived from the desirability that represents the findings.

CONCLUSION

Taking PLGA as the polymer in the experiment and PVA as the stabilizer, a nanoprecipitation process was successfully used to create the different ratios of AL-CUR nanoparticles. To optimize a three-factor, two-level, 5-face-centered design in software Design-Expert trial version was used. Both experiments were analyzed and the optimized nanoparticles had poly dispersibility value and particle size of 75.5 nm and 99.1nm, indicating high stability. The optimized AL-CUR-loaded PLGA nanoparticle with a ratio of 60:120 demonstrated controlled release over an extended length of time in an *in-vitro* drug release investigation. It adheres to anomalous zero-order release kinetics. The produced different ratio of AL-CUR-loaded PLGA nanoparticles might, according to the results, the 60:120 of AL-CUR was better compared to the 60:60 AL-CUR.

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