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Review Article

DESIGN-EXPERT SOFTWARE (DOE): AN APPLICATION TOOL FOR OPTIMIZATION IN PHARMACEUTICAL PREPARATIONS FORMULATION

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ABSTRACT

Formulation is a crucial stage in drug development since it determines the best formula. The quality of the preparation is good and fulfills the standard parameters when using the best formula. This stage is completed through laboratory experiments that take a long time to complete. To address this, software utilizing computer technology, such as software Design Expert, can be used. The goal of this investigation is to see how Design Expert is used in research formulation and optimization. The method of writing a review was carried out by searching Google Scholar and Science Direct with the keywords "Formulation" and "Design Expert," yielding 63 articles, which were then screened using inclusion criteria, notably field of research on formulation optimization accepted for publication between 2011 and April 2020, and exclusion in the form of review articles. The review's findings suggest that the platform is widely utilized and effective at reducing the number of trials, time, and costs associated with formulation development.

Keywords: Formulation, Optimization, Software, Design expert

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INTRODUCTION

Formulation is a preparation activity in pharmaceutical science that focuses on designing the mix of active components and additives after passing pre formulation research. The traditional formulation step in the development of novel medications employs the strategy of modifying one variable or element at a time. Study the effect of composition and process variables on the dosage form first, then adjust one element while keeping another constant. This traditional method, however, has drawbacks, including being inefficient, unpredictable, time-consuming, and unable to describe the interactions that occur [1].

A new strategy was devised to solve the inadequacies of the traditional formulation process, such as the Experimental Design or experimental design, which is an optimization technique. Optimization is required in the preparation formulation process to establish the optimal formula based on the evaluation data of the prepared product. Under some conditions, optimization can be described as a method for obtaining the best mix of product or process attributes. It can also mean choosing the best element or substance from a variety of possibilities [1].

Various approaches are used to process the data from the predetermined assessment parameters. Software allows for more efficient data processing. Predictive data is combined with data generated after the experiment. Design Expert is one of the most extensively used programs [2]. Expert design is utilized for drug delivery system formulations such as extended-release tablets, targeted drug delivery such as liposomes, ethosomes, and nano particles, in addition to traditional medication formulations such as tablets and capsules. Its applications are not restricted to the pharmaceutical industry; for example, the optimization process for studying the ideal composition of vegetable oil mixtures as raw materials for biodiesel synthesis use Design Expert [2].

Because there are options/features that provide direction and can be selected according to the purpose of the design of experiments (DOE) or experimental design to be carried out, the assisted formulation utilizing the Design Expert is more profitable. As a result, a literature review is required to determine the extent to which Design Experts are used in formulations.

METHODS

The preparation of a literature review began on April, 2020, a search using Google scholar and ScinceDirect with the keywords "Formulation" and "Design Expert" resulted in the discovery of 63 articles and 51 were inclusion criteria. The inclusion criteria used in this review article are journals with formulation and optimization research using software Design Expert, journals published between 2011 and April 2020. The exclusion criteria in review are the publication of articles in the form of reviews and optimization articles outside the pharmaceutical, scientific field.

RESULTS AND DISCUSSION

This literature review's findings and discussion are organized into several discussion issues. Paragraphs, figures, and tables are used to present the information.

Design expert

Design Expert is software a statistical method produced by State ease. This was first released in 1996 to help carry out experimental designs such as determining the optimum formula for a preparation. Apart from optimization, software, this can also interpret the factors in the experiment. In software, it this is divided into three choices of research directions depending on the experimental design to be carried out. There are screening, characterization, and optimization options.

Screening requires the least amount of run but provides the least amount of information. Run is the number of experiments that must be carried out according to the selected experimental design. Screening is used if there are many possible factors (>6), but it is not known which one has a real effect. Identification of several important factors using only two levels of each factor and estimates of the main effect (no interaction). Requires follow-up with 2nd DOE to estimate interactions and further requirements.

Characterization requires more runs per factor, but provides more information. Used with only a few factors (<10). Determine which factors have a significant influence on the response, including the interactions between them (fit a two-factor interaction model). Consider adding a midpoint to this design to detect non-linear interactions if you have narrowed down the factors. Given the midpoint, it can be used to find a factor setting that maximizes or minimizes response when no curves are detected.

Optimization requires the most runs per factor, but will provide the most information. Optimization is used after narrowing the list of

factors (<6) that are known to be important and whose optimum likelihood is in the area being tested. Can be used to find factor settings that maximize or minimize the response of the three choices of design of experiments, each of which includes three methods that can be used, namely factorial/response surface, mixture and combined.

Factorial design

Factorial design is an application of regression equations to model the relationship between the response variable and one or more independent variables. Factorial is the most common type of design for process improvement. In research, factorials are used to look for the effects of various conditions on the results of the study and are also used to see the interactions therein. In the factorial design, there are factors, levels and effects. Factor is defined as the amount of the independent variable that will affect the result output or the dependent variable. The factors can be divided into quantitative factors (factors that are numerical, for example, a concentration of 1%, 2%) and qualitative (non-numerical factors. For example, quality/polymer quality). Level is defined as the value or constant for a factor. Effects are changes in response caused by factor-level variations. Responses are defined as the nature or results of the experiment that are observed and can be quantified [3]. The number of research articles with this method consists of 20 research articles.

Response surface methodology (RSM)

Response surface methodology (RSM) is a method that is also known as the Box-Wilson Methodology. Surface methodology responses are a collection of statistical and mathematical techniques that are useful for modeling and analyzing problems where the response is influenced by various variables [4]. Response surface methodology connect a response or outcome variable (output) to the input data (input) that affect it. If an area with an optimum response is found, a model is made to connect to that area so that the analysis can be carried out to achieve the optimal area. In the use of RSM must be in sequence according to the procedure. When a physical event is far from the optimum point, the equation (1) is used. The optimization process with RSM can be seen in fig. 1.

$$y = \beta_0+\beta_1x_1+\beta_2x_2+...+\beta_kx_k+\varepsilon \ldots\ldots (1)$$

Equation (1) is a multiple regression model linear with two independent variables. This independent variable is called the regressor or predictor variable. β_0 is a constant intercept value. β_1 β_2 is a partial regression coefficient where β_1 measures the change in y for every change in x1 units as well as β_2 measures the change in y every change in xunits$_2$. This equation model will bring researchers closer to the optimum area through the optimization path. After the optimum area is found, the second model or equation (2) is used.

$$y = \beta_0+\beta_1x_1+\beta_2x_2+\beta_{11}x_1^2+\beta_{22}x_2^2+\beta_{12}x_1x_2+\varepsilon \ldots\ldots (2)$$

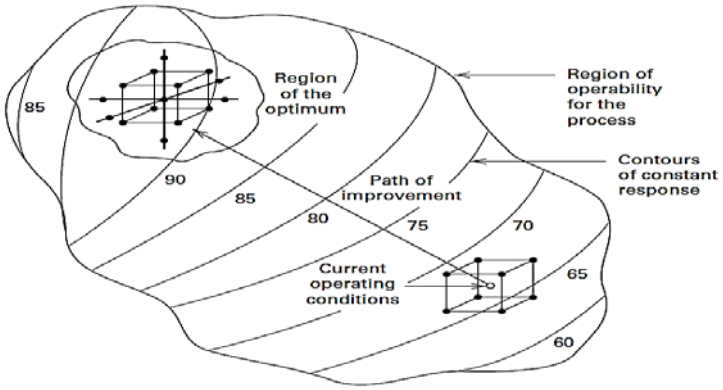

Fig. 1: The optimization process with RSM [4]

The optimization stage is continued by analyzing the response surface to get the optimum point. Analyzes were performed using a suitable response surface. If the matched surface is an estimate of the real response function, then this matched surface analysis will be comparable to the real system. The parameters of the model can be estimated effectively if the experimental design used to collect the data uses an appropriate experimental design.

The response surface design is a design to match the response surface. Matching uses a different design for each model. In RSM there are two designs, namely Central Composite Design (CCD) and Box-Bhenken Design. The number of research articles with this method (Central Composite Design (CCD) and Box-Bhenken Design) there are 26 research articles described in table 1.

Central composite design (CCD)

Central composite design in the optimization process is carried out to determine the approximate optimal direction because the optimization and optimal location are unknown in RSM. In addition, CCD has rotatability or at point x, which is at the same distance, will have (y (x)) the same so it is important to do this. The test points in the CCD are taken based on the test limit values specified for each research factor. The response data obtained are modeled by an appropriate mathematical model. In CCD, there are several models, namely mean, linear, quadratic, 2FI, and cubic. The criteria for selecting the response model are the same as in the selection of models in mixture designs. Determination of the optimum point is seen from the value desaribility resulting. Desirability shows how fulfilled or close to the optimum point. The value desirability close to 1 is the expected value. The optimum point which either has a desirability highor is close to 1 [4].

Box-Bhenken design (BBD)

Box-Bhenken Design (BBD) used for optimization with three independent variables. The Difference Box-Bhenken Design (BBD) with Central Composite Design (CCD), the Box-Bhenken Design trial is more efficient because it has fewer run/experimental units compared to Central Composite Design [5]. Although the number of runs is less, Box-Bhenken is able to predict the optimum value both linear and quadratic well [6, 7].

Design Expert Factorial method is used to find the optimum formula and to determine the interaction between factors, namely the independent variable. The interaction of each variable is used to predict the optimum formula using mathematical calculations in the Design-Expert software. Then the experiment was carried out in the laboratory (wet lab) following the prediction that had been there before. Like in software Design Experts, this independent variable will affect the results on the dependent variable. The value of the dependent variable is used to obtain the optimal formula and compared the actual experimental results with the predicted results of the software. From the research articles in table 1, the method was successfully used to evaluate the effect of formulation variables and improve the optimized formulation, thereby reducing the number of trials, time, and costs of formulation development.

Table 1: Use of design expert with factorial method and RSM (Central composite design and box-bhenken design)

No	Preparation	Optimization variable		Active substance
		Independent variable	Dependent variable	
1	Tablet	Total HPMC K 100M and PVP K30[7]; Carbopol 934 and HPMC K4M [8]; HPMC K4M, ethyl cellulose, and sodium carboxy methyl cellulose [9]; carbopol and Chitosan [10]; OG, HPMC K 15M, Xanthan gum[11]; 8 types of polymers (HPMC K4M, HPMC K15 M, HPMC K100 M, PEO 301, PEO 303, xanthan gum, arabic gum, and alginate)[12]); the number of HPMC K4M and the number of SSG [13]; crospovidone and sodium bicarbonate[14]; Super disintegrant SSG and camphor; sodium starch glycolate and microcrystalline cellulose [15]	Percent of drug released within 1 hour, 8 h, t50% [8]; % drug release, swelling indeks [9]; percentage of drug release in 0.1 N HCL for 2 h and in 6.8 phosphate buffer for up to 24 h[9]; Disintegration time in water and artificial saliva, swelling capacity, dissolution, peak detachment force and permeability[11]; Floating lag time and swelling index[12]; dissolution at 6 h, [14] hours, and 24 h[13]; time lag and% drug release [14]; friability and breakdown time; disintegration time and water absorption ratio[15]; Disintegration time and drug release t90% [16]	Itopride HCL [8]; Aceclofenac [9]; Losartan [10]; Repaglinide [11]; Ivy Leaves [12]; Ketoprofen [13]; Montelukast sodium [14]; Pacing extract [15]; Risperidone [16];
2	Emulgel	Emulsifier concentration and Carbopol Concentration	Percent cumulative drug release at 2 h and% cumulative drug release at 6 h.	Peroxicam [17]
3	Transdermal patches	Concentration matrix Polymer, Plasticizer, di-N-butyl phthalate, and Permeation enhancer, Almond oil (% w/w)[17]; levulinic acid (LEV), lauryl alcohol (LA), and Tween 80 (T)[18]; Phospholipids%, ethanol%,% terpenes, and terpene types[19]; lipid ratio (soy lecithin: cholesterol), the lipid ratio and surfactants, surfactant ratio (Tween 80: sodium deoxycholate)[20]; solid and liquid lipid ratio, tween ratio of 80 and span 80 and number of HPH cycles[21]; ethanol concentration, total cholesterol (CHO) and soybean phosphatidylcholine (SPC) [22].	Stable flux, time delay, permeability coefficient (kp) [18]; skin permeation, tack value, and skin strength [19]; Vesicle size (invasom) and the entanglement efficiency of AVA[19]; flow absorption (permeationflux) [21]; particle size, PDI, zeta potential and encapsulation efficiency [22]; encapsulation efficiency (EE), vesicle size (VS), zeta potential (ZP) and polydispersity index (PDI)[23]	Dexibuprofen [18]; Buprenorphine [19]; Avanafil [20]; Insulin [21]; Rivastigmine[221]; Paeonol [23]; Ketorolac tromethamine [24]; Olmesartan medoxomil [25].
4	Filling granules	crushing (Avicel PH 101) and binding agent (PVP K-30)	Flow rate, absorption, moisture and determination index of	Gotu kola extract and herba Sambiloto [26].
5	Gel in situ	lecithin concentration, Tween 80, and d-tocopherol polyethylene glycol succinate (TPGS) [26]; type of Eudragite polymer and the amount of polymer used [27]; concentration of gellan gum and carbopol 934[28]; Total phytantriol, the amount of Lutrol, and the pH of the hydration medium [29]; GMS and Tween 80 concentrations [30]; Oil concentration to Smix and gellan gum ratio [31]; polymer percentage, PF-127 and PF-68 alendronate polymer [32]	Particle size, entrapment, and stability[27]; Particle size, zeta potential and EE% [28]; viscosity under non-physiological conditions, Viscosity at physiological conditions [29]; particle size, encapsulation ulation, andflux steady state (Alharbi and Hosny, 2020); particle size, PDI, zeta potential (ZP) and% entrapment efficiency (EE) [31]; *in vitro* drug release and viscosity at physiological pH [32]; Gelation temperature (°C), gelation time (seconds), syringe test (seconds), *in vitro* drug release studies (% cumulative drug release) alendronate[33]	Rosuvastatin-Ellagic Acid [27]; fluconazole-hydroxypropyl-beta-cyclodextrin complex [28]; Midazolam hydrochloride [29]; ciprofloxacin [30]; Bimatoprost [31]; Lorazepam [32]; alendronate [33]; Ropinirole [34]; Sumatriptan succinate [35]; Moxifloxacin hydrochloride [36].
6	suspension	Carbopol 934 and PGA	Viscosity, sedimentation volume, and redispersibility of	Ciprofloxacin [37]
7	Ocular Insert	Concentrations of CAB (1, 2 and 3% w/v) and PEG-600 (0, 30 and 60% w/w of dry weight CAB) in polymer solution before casting; concentrations of poloxamer 407 and PG[37]; Cumulative drug release percentage, thickness [37]; Lipid ratio (soy lecithin ratio to cholesterol and drug to lipid ratio [38]; gellan gum, carbopol 934P and benzododecenium bromide [39]	Drug release *in vitro* at the end of 24 h, rate constant first order and time required for 50% brimonidine tartrate to be released [38]; crease resistance of prepared inserts [38]; drug trapping efficiency (%), drug loading (%) and particle size (nm) [39]; maximum viscosity, mucoadhesive strength, permeability coefficient and slow release of drug release [40]	Brimonidine tartrate [38]; Dorzolamide Hydrochloride [41]; Besifloxacin hydrochloride [39], [40], [42]–[44]
8	Self-nanoemulsifying Drug Delivery System (Snedds)	Surfactants, co-surfactants, and oil ak [44]; surfactant (Cremophor® EL), co-surfactant (Capmul® MCM-C8) and oil phase (lemon essential oil: Permata; 1: 1) [45]	Emulsion droplet size, PDI, % drug loading and zeta potential [45]; globule size (R1) and% encapsulation efficiency (R2 BCT and R2 HSP) hesperetin [46]; Visual characterization, turbidity, average droplet size, polydispersity index [47]	Polypeptide-k [45]; Bioflavonoid hesperetin [46]; Gemfibrozil [47, 51]

Mixture design

Mixture is used for components in a formulation that change proportionally to each other. The percentage of each variable must always increase to get a fixed total value, for example, 100 percent by weight. Even if there are a very small number of variable components, they can still be used because this method shows a very sensitive response to these substances. Example: A food scientist experimenting with a fruit mixture consisting of watermelon, pineapple and orange juice, and water. The response depends on the proportions of the various fruits, not the total amount of the mixture. If the amount of each ingredient is doubled, the taste remains the same.

The factor value in the mixture design has a proportion between 0 and 1. One of the methods in the mixture design is simplex lattice design (SLD). Simplex lattice design is an optimization method used to determine the optimum formula for a mixture of ingredients with

the proportion of the total amount of a different ingredient being 1 (100%). The materials or factors used in the optimization consist of at least two different materials. The factor in the mixture design will determine the design space or test area.

The test area for each factor is constrained by the maximum number of materials that can be employed for that factor. The minimum and maximum limitations for each factor were used. The software will identify the test spots on the formula based on the test area. As test points, the software will employ the verticles, edge centers, overall centroid, and check runs. It will be repeated or copied at some point in order to obtain the value pure error. A contour plot or contour plot will also be used to describe the answer achieved. With contour plots, precise optimal spots can be found.

A mathematical model is used to model data; there are four mathematical models for mixture design: linear, quadratic, cubic, and special cubic. During the ANOVA analysis, the model is chosen based on numerous criteria, including the model's significance, the significance of the lack of fit, adjusted-square, and anticipated r-square. The model is chosen if it has a model probability of less than 5% and a probability of lack of fit of less than 5%, indicating that the model has a significant effect on the response at the 5% significance level [4]. The number of research articles with this method there are 7 research articles which are described in table 2.

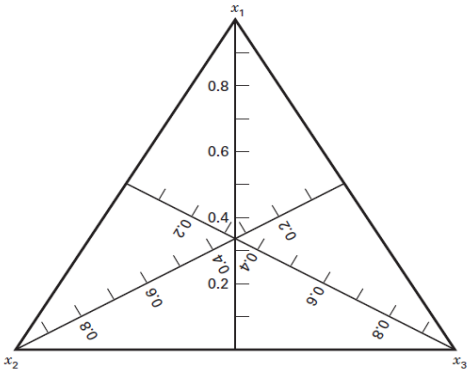

Fig. 2: Test area mixture design with three factors [4]

Table 2: The use of design expert method mixture design in the formulation of several pharmaceuticals

No	Preparations	Variable optimization	Active substances
1	Transdermal patches	Optimal mix ratio of BIO-PSA 7-4302 silicone adhesive, DuroTak polyacrylic adhesive 387-2287, oleylalcohol and ibuprofen [52]	Ibuprofen [52]; Ketoprofen [53]
2	Tablets	Avicel® PH 200 and Amylum;	Pacing extract [54]
3	Self-nanoemulsifying Drug Delivery System (Snedds)	Composition of surfactants, co-surfactants, and oil [55, 57]	Pentagamavunon-0[55]; Mangosteen Peels [56, 57]
4	Syrup	Glycerin,sorbitol solution 70%, and 0.5% CMC-Na	mucilago of Hibiscus Flower Fraction [58]

Mixture Design can provide optimal formulas by using response data from the parameters of each preparation. From various variations of the mixed formula, the optimum formula is a formula that has the evaluation results within the limit range in each parameter. Then seen using the degree of desirability, a formula that has a degree of desirability close to 1 is the best formula/optimum. Of the 7 articles in table 2 each preparation has optimal results with alevel desirability close to 1. These results indicate that Mixture Design can be used for formula optimization with a high level of confidence.

Combined

Combined or combination is a design of experiment (DOE) combination between factorial/RSM with the mixture. Used to study the variables between the variable composition and process variables in one DOE.

The use of design expert in liquid, semisolid, and solid formulation

Software Design Expert with the various facilities provided makes many researches on the latest formulations tend to use the software. In addition to the research articles detailed in table 1 and table 2, there are still several research articles on liquid, semi-solid and solid dosage formulations with synthetic active substances and natural ingredients, which are presented by software Design Expert which are described in tables 3 and 4.

Table 3: Optimized tablet preparation with design expert

Active substance	Method	Variable optimization		Reference
		Independent variable	dependent variable	
Pacing (*Costus speciosus*) Extract	Simplex lattice design	Avicel® PH 200 and Amylum	Friability and disintegration time	[54, 55]
Levocetirizine hydrochloride and ambroxol hydrochloride	Central composite design	Super disintegrant SSG and camphor	disintegration time and water absorption ratio	[15]
Montelukast sodium	Response surface methodology	Crospovidone and sodium bicarbonate	Friability and disintegration time	[14]
ketoprofen	3^2 factorial design	HPMC K4M and total SSG	pause time and% drug release.	[13]
Aceclofenac tablets (100 mg)	Response Surface Methodology	Avicel PH 102, Magnesium Stearate, and AcDiSol	Variations in weight, brittleness, disintegration and dissolution.	[9]
ivy leaf extract	Response Surface Methodology	Sustaining polymer, 8 types of polymers (HPMC K4M, HPMC K15 F, HPMC K100 M, PEO 301, PEO 303, xanthan gum, arabic gum, and alginate)	Dissolution in 6 h, 12 h, and 24 h.	[12]
repaglinide	Factorial (three full level factorial design)	OG, HPMC K 15M, Xanthan gum	Floating lag time and swelling index	[11]
Effect of polymer type on characteristics of buccal tablets using factorial design	Factorial design	Carbopol and Chitosan	Time disintegration in water and artificial saliva, swelling capacity, dissolution, peak detachment force and permeability	[59]
Losartan Potassium	Response Surface Methodology	HPMC K4M (X1), ethyl cellulose (X2), and sodium carboxy methyl cellulose (X3)	percentage of drug release in 0.1 N HCL for 2 h (Y1) and in 6.8 phosphate buffer for up to 24 h (Y2)	[10]
Risperidone	Factorial design	Sodium starch glycolate and microcrystalline cellulose.	Disintegration time and drug release t90%.	[16]

Table 4: Solid, Semisolid, Liquid preparations other than tablets optimized by design expert

Types of preparations	The active substance
Suspension	Ciprofloxacin [37]
Syrup	Hibiscus Flower Fraction [58]
Granules	Herba Gotu kola Extract and Herba sambiloto [26]

Use of design expert in formulations

The drug delivery system

Use of the software is Design Expert not limited to conventional dosage formulations such as tablets, capsules, and emulsion. There have been many studies on the development of drug delivery systems with the help of software Design Expert. In addition to conventional dosage formulations such as tablets, table 5, 6, 7, 8 is a formulation Drug Delivery System with optimization using a Design Expert.

Table 5: Optimized transdermal delivery with design expert

Active substance	Method	Optimization variable		Reference
		Independent variable	Dependent variable	
buprenorphine	Response surface methodology (Box-Bhenken design)	levulinic acid (LEV), lauryl alcohol (LA), and Tween 80 (T)	Skin permeation, tack value, and skin strength.	[19]
avanafil	Response surface methodology (Box-bhenken design)	Phospholipid%, ethanol%, terpene%, and terpene types.	Vesicle size (invasome) and AVA entrapment efficiency	[20]
insulin	Factorial design	Process parameters such as lipid ratio (soy lecithin: cholesterol), lipid and surfactant ratio, surfactant ratio (Tween 80: sodium deoxycholate)	to variables flow-dependent absorption(permeationflux)	[21]
rivastigmine	Response Surface Methodology (Box-Bhenken Design)	Solid and liquid lipid ratio, tween ratio 80 and span 80 and number of HPH cycles.	Particle size, PDI, zeta potential and encapsulation efficiency	[22]
Paeonol	Central composite design	Ethanol concentration, total cholesterol (CHO) and soybean phosphatidylcholine (SPC).	Encapsulation efficiency (EE), vesicle size (VS), zeta potential (ZP) and polydispersity index (PDI)	[23]
Transdermal delivery system	Mixture design	Optimal mix ratio of BIO-PSA silicone adhesive 7-4302, DuroTak 387-2287 polyacrylic adhesives, oleylalcohol and ibuprofen		[52]
anti-rheumatic dexibuprofen	Response Surface Methodology (Box-Bhenken Design)	Concentration of Polymer matrix, Plasticizer, di-N-butyl phthalate, and Permeation enhancer, Almond oil (% w/w).	Stable state flux, time delay, permeability coefficient (kp)	[18]
Ketoprofen	Simplex lattice design	Oil phase, emulsifier phase and water phase		[53]
Ketorolac tromethamine	Central composite design	Carbopol 940 and PEG 400.	% Cumulative drug permeation	[24]
Olmesartan medoxomil	Box-Behnken design	Phospholipid, ethanol, and b-citronellene,	Vesicle size, entrapment efficiency, transdermal flux	[25]

From table 5 it can be concluded that in the optimization of the transdermal route preparation, the important point in the optimization is the composition of the matrix. The matrix will affect the skin permeation value, tack value, vesicle size (VS), zeta potential (ZP) and polydispersity index (PDI).

Table 6: In situ gel optimized by design expert

Active substance	Method	Optimization variable		Reference
		Independent variable	Dependent variable	
Rosuvastatin-Ellagic Acid	Response Surface Methodology (Box-Bhenken Design)	Concentration of lecithin, Tween 80, and d-tocopherol polyethylene glycol succinate (TPGS)	Variable dependent Particle size, entrapment and stability.	[27]
fluconazole-hydroxypropyl-beta-cyclodextrin complex	Factorial design of the	type of polymer Eudragite and the amount of polymer used	Particle size, zeta potential and EE%.	[28]
Midazolam hydrochloride	Factorial design	concentration of gellan gum and carbopol 934	Viscosity under non-physiological conditions, Viscosity under physiological conditions.	[29]
ciprofloxacin	Response Surface Methodology (Box-Bhenken Design)	Total phytantriol, amount of Lutrol, and pH of hydration media.	Particle size, encapsulation, and flux steady state.	[30]
Bimatoprost solid lipid nanoparticles	Factorial design	Concentration of GMS and Tween 80	Particle size, PDI, zeta potential (ZP) and % trap efficiency (EE)	[31]
Lorazepam	Factorial design	Oil concentration to Smix and gellan gum ratio.	*In vitro* drug release and viscosity at physiological pH.	[32]
Alendronate	Factorial design	Percentage of polymer, PF-127 and PF-68 polymer.	Gelation temperature (° C), gelation time (seconds), syringe test (seconds), *in vitro* drug release studies (% cumulative drug release)	[33]

Active substance	Method	Optimization variable		Reference
		Independent variable	Dependent variable	
Ropinirole	Factorial design	PF 127 concentration and HPMC K4M concentration.	Drug release at 5 h, gelation temperature and mucoadhesive strength	[34]
Sumatriptan succinate	Factorial design	Gellan gum% w/v and PEG 400% w/v	Viscosity, mucoadhesive strength, % cumulative drug release	[35]
Moxifloxacin hydrochloride	Factoriall design	Concentration of PF68 and Gelrite (cation sensitive in in situ gelling, hydrophilic and mucoadhesive polymers)	Gelation temperature (GT in °C), gel strength (GS in s), bioadhesion force (BF in N), viscosity (h in Pa) and cumulative drug release after 1 and 10 h	[35]

From table 6 it can be concluded that in the optimization of gel preparations in situ, the important points in optimization are the selection of polymers and the quantity used. The polymer will affect gelation temperature (° C), gelation time (seconds), syringe test (seconds), *in vitro* drug release studies (% cumulative drug release)

Table 7: Ocular insert optimized with design expert

Active substance	Method	Optimization		Reference
		Variable independent	Variable dependent variable	
Brimonidine tartrate	Response surface methodology	Concentrations of CAB (1, 2 and 3% w/v) and PEG-600 (0, 30 and 60% w/w of dry weight of CAB) in the polymer solution before casting were treated as independent variables.	*In vitro* drug release at the end of 24 h (Y1), first-order rate constant (Y2) and time required for 50% brimonidine tartrate to be released	[38]
Dorzolamide hydrochloride	Factorial design	Concentration of poloxamer 407 and PG.	Percentage of cumulative drug release, thickness and fold resistance of prepared inserts	[41]
Besifloxacin hydrochloride	Factorial design	Lipid ratio (ratio of soy lecithin to cholesterol and ratio of drug to lipid	Efficiency of drug entrapment (%), drug loading (%) and particle size (nm)	[39]
a novel in situ gel for sustained ocular drug delivery	Response Surface Methodology (Box-Bhenken Design)	Gellan gum, carbopol 934P and benzododecenium bromide.	Maximum viscosity, mucoadhesive strength, permeability coefficient and sustained release drug release.	[40]
Terconazole	Factorial design	Amount of bile salts (mg), type of peripheral activator (Cremophor EL, Cremophor RH 40), Amount of edge activator (mg).	Percent entrapment efficiency; particle size, polydispersity index, zeta potential.	[42]
Fluconazole	Box-Behnken Design	Chitosan concentration, NaTPP concentration and NaTPP volume.	Encapsulation efficiency, loading capacity and average particle diameter	[43]
Clonidine hydrochloride	Factorial design	Clonidine Hydrochloride gel with the amount of Poloxamer 407 (%) and polymer (% HPMC K15M).	Gelation temperature, drug content, bioadhesive strength, viscosity.	[44]

From table 7 it can be concluded that in the optimization of ocular insert preparations, the important points in the optimization are the selection of polymers and the amount used. The polymer will have an effect on *in vitro* drug release at the end of 24 h, a first-order rate constant and the time required for 50% of the active substance to be released.

Table 8: Self-nanoemulsifying drug delivery system (snedds) optimized by design expert

Article title	Method	Optimization variable		Reference
		Independent variable	Dependent variable	
(*Garcinia Mangostana L.,)*	Simplex Lattice Design	Composition of surfactants, co-surfactants, and oils		[58]
Anti-inflammatory agent pentagamavunon-0	Simplex Lattice Design	Composition of surfactants, co-surfactants, and oils		[59]
Polypeptide-k	Response Surface Methodology (Box-Bhenken Design)	Surfactants, co-surfactants, and oils.	Emulsion droplet size, PDI, % drug loading and zeta potential.	[45]
Bioflavonoid hesperetin	Central composite design	Amount of oil, amount of surfactant and amount of co-surfactant	globule size and% efficiency of BCT and HSP encapsulation)	[46]
Gemfibrozil	Response Surface Methodology (Box-Bhenken Design)	surfactant (Cremophor® EL), co-surfactant (Capmul® MCM-C8) and oil phase (lemon essential oil: Gem; 1: 1)	Visual characterization, turbidity, average droplet size, polydispersity index.	[47]
Atazanavir	Central composite design	Total lipids and surfactants.	Globule size and% dissolution efficiency in 30 min	[48]
Flurbiprofen	Box–Behnken Design	Capryol PGMC, Tween 20, and Transcutol HP.	size, equilibrium solubility, and cumulative percentage of drug released in 15 min	[49]
Embelin	Box-Behnken design	X1 (amount of oil; Capryol 90), X2 (amount of surfactant; Acrysol EL 135) and X3 (number of co-surfactants; PEG 400).	Emulsifying time, grain size and drug release.	[50]
Glipizide	Central composite design	Captex 355, Solutol HS15, and Imwitor 988.	Drip size (nm), turbidity, and percent transmittance	[51]
Furosemide	Simplex Lattice Design	Capryol-90, polysorbate-80, and PEG-400		[60]

From table 8 it can be seen that in the optimization of the Self-nano emulsifying Drug Delivery System (SNEDDS) preparation, the selection of oil and surfactants affects the concentration used and the optimal conditions of the formula. The optimum formula is selected based on the turbidity value, the average droplet size and the polydispersity index of the preparation.

Percent prediction error

Percent prediction error is a value to measure the prediction error of an analytical method. In this review, not all journals include values prediction error. The prediction error acceptable value is<4%. As in the research of Choudhury *et al.*, [14] the value of prediction error the dependent variable is in the range of 2-3.5%, which means that it still fulfills the requirements that this method is the right method for analyzing the research carried out.

CONCLUSION

It may be concluded that Design Expert software is effective in formulation since it makes determining the best formula easier for the formulator. Using various methodologies, software can be used to evaluate the effect of formulation factors for each preparation. As a result, the experiment's design has both advantages and downsides. DOE with Design Expert has the advantage of reducing the number of trials and the time required to produce formulas. The reliance on software as an optimization tool is a limitation of DOE with Design Expert, which results in a value prediction error of less than 4%.

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CONFLICT OF INTERESTS

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REFERENCES

1. Singh BS, Kapil R, Ahuja N. Systematic optimisation of drug delivery systems: an insight. Pharm Rev. 2008:146-86.
2. Ramadhani RA, Riyadi DHS, Triwibowo B, Kusumaningtyas RD. Review pemanfaatan design expert untuk optimasi komposisi campuran minyak nabati sebagai bahan baku sintesis biodiesel. J Tek Kim Ling. 2017 Oct;1(1):1. doi: 10.33795/jtkl.v1i1.5.
3. Bolton S, Bon C. Pharmaceutical statistics: practical and clinical applications. 4th ed. Rev. expanded. ed, Drugs and the pharmaceutical sciences. 4th ed. New York: M. Dekker; 2004.
4. Montgomery DC. Design and analysis of experiments. 9th ed. Wiley; 2017.
5. Purwanti EP, Ferihan P. Optimasi parameter proses pemotonhgan stainless stell sus 304 untuk kekasaran permukaan dengan metode respon surface. Prosiding seminar nasional matematika dan pendidikan matematika. Penguatan peran matematika dan pendidikan matematika untuk Indonesia yang lebih Baik; 2013. Available: http://uny.ac.id [Last accessed on 19 May 2021]
6. Perincek O, Colak M. Use of experimental box-behnken design for the estimation of interactions between harmonic currents produced by single phase loads. Int J Eng Res Appl. 2012;3:58-165.
7. Sopyan I, Wahyuningrum R, KS IS. An experimental design in the optimization of various tablet excipient formulations- a concise review. Int J App Pharm 2022;14:28-32. doi: 10.22159/ijap.2022v14i1.43380.
8. Bose A, Wong TW, Singh N. Formulation development and optimization of sustained release matrix tablet of itopride HCl by response surface methodology and its evaluation of release kinetics. Saudi Pharm J. 2013;21(2):201-13. doi: 10.1016/j.jsps.2012.03.006. PMID 23960836.
9. Rabia B. Formulation design and optimization of aceclofenac tablets (100 mg) using central composite design with response surface methodology. Lat Am J Pharm. 2014;33:1009-18.
10. Reddy YD, Chetty CM, Kumar KR, Dachinamoorthi D. Formulation and optimization of extended release matrix tablets of losartan potassium using response surface methodology (RSM). J Pharm Res Int. 2017;19(5):1-12. doi: 10.9734/JPRI/2017/36668.
11. Naveen NR, Gopinath C, Rao DS. Design expert supported mathematical optimization of repaglinide gastroretentive floating tablets: *in vitro* and *in vivo* evaluation. Future J Pharm Sci. 2017;3(2):140-7. doi: 10.1016/j.fjps.2017.05.003.
12. Na YG, Jeon SH, Byeon JJ, Kim MK, Lee HK, Cho CW. Application of statistical design on the early development of sustained-release tablet containing ivy leaf extract. J Drug Deliv Sci Technol. 2019;54:1013-9. doi: 10.1016/j.jddst.2019.101319.
13. Khadabadi DSS, Chishti N, Khan FM, Tadvee AA. Formaulation and evaluation of press coated tablet of ketopropen–a cronotheurapeutics approach. | Semantic Scholar. 2013. Available from: https://www.semanticscholar.org/paper/formulation-andevaluation-of-press-coated-tablet-%E2%80%93Khadabadi-chishti/e00ff15ccc64ec941af10bb85c91578da7a87e1b.
14. Usman S, Ejaz RR, Safdar KA. Formulation development and optimization of orally disintegrating tablets of montelukast sodium by design-expert. Trop J Pharm Res. 2018;17(9). doi: 10.4314/tjpr.v17i9.3.
15. Choudhury P, Deb P, Dash S. Formulation and staitistical optimazation of bilayer sublingual tablet of levocetrizine hydrochloride and ambroxol hydrochloride. Asian J Pharm Clin Res. 2016:228-34. doi: 10.22159/ajpcr.2016.
16. Sarkhejiya NA, Khachar KK, Patel PP. Formulation development and evaluation of sublingual tablet of risperidone. Res J Pharm Technol. 2013;6(4):428-34.
17. Khunt D, Mishra A, Shah D. Formulation design and development of piroxicam emulgel. Int J PharmTech Res. 2012;4:1332-44.
18. Akhlaq M, Arshad MS, Mudassir AM, Hussain A, Kucuk I, Haj-Ahmad R. Formulation and evaluation of anti-rheumatic dexibuprofen transdermal patches: a quality-by-design approach. J Drug Target. 2016;24(7):603-12. doi: 10.3109/1061186X.2015.1116538, PMID 26586147.
19. Taghizadeh SM, Moghimi Ardakani A, Mohamadnia F. A statistical experimental design approach to evaluate the influence of various penetration enhancers on transdermal drug delivery of buprenorphine. J Adv Res. 2015;6(2):155-62. doi: 10.1016/j.jare.2014.01.006. PMID 25750749.
20. Ahmed OAA, Badr-Eldin SM. Development of an optimized avanafil-loaded invasomal transdermal film: *ex vivo* skin permeation and *in vivo* evaluation. Int J Pharm. 2019;570:118657. doi: 10.1016/j.ijpharm.2019.118657. PMID 31491483.
21. Malakar J, Sen SO, Nayak AK, Sen KK. Formulation, optimization and evaluation of transferosomal gel for transdermal insulin delivery. Saudi Pharm J. 2012;20(4):355-63. doi: 10.1016/j.jsps.2012.02.001. PMID 23960810.
22. Chauhan MK, Sharma PK. Optimization and characterization of rivastigmine nanolipid carrier loaded transdermal patches for the treatment of dementia. Chem Phys Lipids. 2019;224:104794. doi: 10.1016/j.chemphyslip.2019.104794. PMID 31361985.
23. Ma H, Guo D, Fan Y, Wang J, Cheng J, Zhang X. Paeonol-loaded ethosomes as transdermal delivery carriers: design, preparation and evaluation. Molecules. 2018;23(7). doi: 10.3390/molecules23071756, PMID 30018278.
24. Nanda S, Saroha K, Sharma B. Formulation, evaluation and optimization of transdermal gel of ketorolac tromethamine using face centered central composite design. Int J Pharm Pharm Sci. 2014;6:133-9.
25. Kamran Mohd, Ahad A, Aqil Mohd, Imam SS, Sultana Y, Ali A. Design, formulation and optimization of novel soft nano-carriers for transdermal olmesartan medoxomil delivery: *in vitro* characterization and *in vivo* pharmacokinetic assessment. Int J Pharm. 2016;505(1-2):147-58. doi: 10.1016/j.ijpharm.2016.03.030, PMID 27005906.
26. Widyastuti L, Pramono S. Formulasi granul kombinasi ekstrak terpurifikasi herba Pegagan (Centella asiatica (L.) Urban) dan Herba sambiloto (Andrographis paniculata (Burm. f.) Nees) [thesis]. Yogyakarta: Universitas Gadjah Mada; 2013. Available from: http://etd.ugm.ac.id/index.php?mod=penelitian_detailandsub=PenelitianDetailandact=viewandtyp=htmlandbuku_id=66270.

27. Hosny KM, Rizg WY, Khallaf RA. Preparation and optimization of *in situ* gel loaded with rosuvastatin-ellagic acid nanotransfersomes to enhance the anti-proliferative activity. Pharmaceutics. 2020;12(3). doi: 10.3390/pharmaceutics12030263, PMID 32183144.
28. Elmotasem H, Awad GEA. A stepwise optimization strategy to formulate in situ gelling formulations comprising fluconazole-hydroxypropyl-beta-cyclodextrin complex loaded niosomal vesicles and Eudragit nanoparticles for enhanced antifungal activity and prolonged ocular delivery. Asian J Pharm Sci. 2020;15(5):617-36. doi: 10.1016/j.ajps.2019.09.003. PMID 33193864.
29. Patel S, Koradia H, Parikh R. Design and development of intranasal in situ gelling system of midazolam hydrochloride using 32 full factorial design. J Drug Deliv Sci Technol. 2015;30:154-62. doi: 10.1016/j.jddst.2015.10.010. jddst.2015.10.010.
30. Alharbi WS, Hosny KM. Development and optimization of ocular in situ gels loaded with ciprofloxacin cubic liquid crystalline nanoparticles. J Drug Deliv Sci Technol. 2020;57:101710. doi: 10.1016/j.jddst.2020.101710.
31. Wadetwar RN, Agrawal AR, Kanojiya PS. In situ gel containing Bimatoprost solid lipid nanoparticles for ocular delivery: *in vitro* and *ex-vivo* evaluation. J Drug Deliv Sci Technol. 2020;56:10175. doi: 10.1016/j.jddst.2020.101575.
32. Shah V, Sharma M, Pandya R, Parikh RK, Bharatiya B, Shukla A. Quality by Design approach for an in situ gelling microemulsions of lorazepam via intranasal route. Mater Sci Eng C Mater Biol Appl. 2017;75:1231-41. doi: 10.1016/j.msec.2017.03.002. PMID 28415411.
33. Das T, Venkatesh MP, Pramod Kumar TM, Koland M. SLN based alendronate in situ gel as an implantable drug delivery system–a full factorial design approach. J Drug Deliv Sci Technol. 2020;55:101415. doi: 10.1016/j.jddst.2019.101415.
34. Rao M, Agrawal DK, Shirsath C. Thermoreversible mucoadhesive *in situ* nasal gel for treatment of Parkinson's disease. Drug Dev Ind Pharm. 2017;43(1):142-50. doi: 10.1080/03639045.2016.1225754, PMID 27533244.
35. Galgatte UC, Kumbhar AB, Chaudhari PD. Development of in situ gel for nasal delivery: design, optimization, *in vitro* and *in vivo* evaluation. Drug Deliv. 2014;21(1):62-73. doi: 10.3109/10717544.2013.849778, PMID 24191774.
36. Shastri DH, Prajapati ST, Patel LD. Thermoreversible mucoadhesive ophthalmic *in situ* hydrogel: design and optimization using a combination of polymers. Acta Pharm. 2010;60(3):349-60. doi: 10.2478/v10007-010-0029-4, PMID 21134868.
37. Sainah. Optimasi formula suspensi siprofloksasin dengan kombinasi pulvois gummi arabicum (PGA) dan karbopol 934 manggunakan metode desain faktorial. Jurnal Mahasiswa Farmasi Fakultas Kedokteran Untan; 2021.
38. Shivakumar HN, Desai BG, Subhash PG, Ashok P, Hulakoti B. Design of ocular inserts of brimonidine tartrate by response surface methodology. J Drug Deliv Sci Technol. 2007;17(6):421-30. doi: 10.1016/S1773-2247(07)50083-3.
39. Bhattacharjee A, Das PJ, Dey S, Nayak AK, Roy PK, Chakrabarti S. Development and optimization of besifloxacin hydrochloride loaded liposomal gel prepared by thin film hydration method using 32 full factorial design. Colloids Surf A Physicochem Eng Aspects. 2020;585:124071. doi: 10.1016/j.colsurfa.2019.124071.
40. Ranch KM, Maulvi FA, Naik MJ, Koli AR, Parikh RK, Shah DO. Optimization of a novel *in situ* gel for sustained ocular drug delivery using box-behnken design: *in vitro*, *ex vivo*, *in vivo* and human studies. Int J Pharm. 2019;554:264-75. doi: 10.1016/j.ijpharm.2018.11.016, PMID 30423418.
41. Patil SS, Bade A, Tagalpallewar A. Design, optimization and pharmacodynamic comparison of dorzolamide hydrochloride soluble ocular drug insert prepared by using 32 factorial design. J Drug Deliv Sci Technol. 2018;46:138-47. doi: 10.1016/j.jddst.2018.05.010.
42. Abdelbary AA, Abd-Elsalam WH, Al-Mahallawi AM. Fabrication of novel ultra deformable bilosomes for enhanced ocular delivery of terconazole: *in vitro* characterization, *ex vivo* permeation and *in vivo* safety assessment. Int J Pharm. 2016;513(1-2):688-96. doi: 10.1016/j.ijpharm.2016.10.006. PMID 27717916.
43. Chopra AK, Marwaha RK, Kaushik D, Dureja H. Box-behnken designed fluconazolel chitosan nanoparticles for ocular delivery. Sci Technol. 2014;3:1. doi: 10.4172/2325-9604.1000121
44. Avinash K, Ajay S. Formulation and evaluation of thermoreversible *in situ* ocular gel of clonidine hidrocloride glaucomma-pharmacophore. Com/en/article/formulation-and-evaluation-of-thermoreversible-in-situ-ocular-gel-of-clonidine-hydrochloride-for-glaucoma; 2015.
45. Garg V. Solid self-nanoemulsifying drug delivery systems for oral delivery of polypeptide-k: formulation, optimization, *in vitro* and *in vivo* antidiabetic evaluation. Eur J Pharm Sci. 2017;109:297-315. doi: 10.1016/j.ejps.2017.08.022, PMID 28842349.
46. Arya A, Ahmad H, Tulsankar S, Agrawal S, Mittapelly N, Boda R. Bioflavonoid hesperetin overcome bicalutamide induced toxicity by co-delivery in novel SNEDDS formulations: optimization, *in vivo* evaluation and uptake mechanism. Mater Sci Eng C Mater Biol Appl. 2017;71:954-64. doi: 10.1016/j.msec.2016.11.006. PMID 27987794.
47. Villar AMS, Naveros BC, Campmany ACC, Trenchs MA, Rocabert CB, Bellowa LH. Design and optimization of self-nanoemulsifying drug delivery systems (SNEDDS) for enhanced dissolution of gemfibrozil. Int J Pharm. 2012;431(1-2):161-75. doi: 10.1016/j.ijpharm.2012.04.001. PMID 22498011.
48. Singh G, Pai RS. Optimized self-nanoemulsifying drug delivery system of atazanavir with enhanced oral bioavailability: *in vitro*/*in vivo* characterization. Expert Opin Drug Deliv. 2014;11(7):1023-32. doi: 10.1517/17425247.2014.913566, PMID 24820316.
49. Marasini N, Yan YD, Poudel BK, Choi HG, Yong CS, Kim JO. Development and optimization of self-nanoemulsifying drug delivery system with enhanced bioavailability by Box-Behnken design and desirability function. J Pharm Sci. 2012;101(12):4584-96. doi: 10.1002/jps.23333, PMID 23023800.
50. Parmar K, Patel J, Sheth N. Self nano-emulsifying drug delivery system for Embelin: Design, characterization and in-vitro studies. Asian J Pharm Sci. 2015;10(5):396-404. doi: 10.1016/j.ajps.2015.04.006.
51. Dash RN, Mohammed H, Humaira T, Ramesh D. Design, optimization and evaluation of glipizide solid self-nanoemulsifying drug delivery for enhanced solubility and dissolution. Saudi Pharm J. 2015;23(5):528-40. doi: 10.1016/j.jsps.2015.01.024, PMID 26594119.
52. Michaelis M, Leopold CS. Mixture design approach for early stage formulation development of a transdermal delivery system. Drug Dev Ind Pharm. 2015;41(9):1532-40. doi: 10.3109/03639045.2014.971029, PMID 25308745.
53. Duangjit S, Mehr LM, Kumpugdee Vollrath M, Ngawhirunpat T. Role of simplex lattice statistical design in the formulation and optimization of microemulsions for transdermal delivery. Biol Pharm Bull. 2014;37(12):1948-57. doi: 10.1248/bpb.b14-00549. PMID 25590086.
54. Damayanti D, Sari IP, Sulaiman TNS, Bestari AN, Setiawan IM. The formulation of pacing (Costus speciosus) extract tablet by using Avicel®Ph 200 as filler-binder and amylum as disintegration agent. Indonesian J Pharm. 2018;29(1). doi: 10.14499/indonesianjpharm29iss1pp29.
55. Dewantara Putra IGNA, Murwanti R, Rohman A, Sulaiman TNS. Optimizing formulation of mini tablets floating ranitidine HCl using fully pregelatinized starch (Manihot esculenta crantz) with simplex lattice design. Int J App Pharm. 2019;11(4):32-40. doi: 10.22159/ijap.2019v11i4.32657.
56. Astuti IY, Marchaban M, Martien R, Nugroho AE. Design and optimization of self nano-emulsifying drug delivery system containing a new anti-inflammatory agent pentagamavunon-0. Indones J Chem. 2017;17(3). doi: 10.22146/ijc.22640.
57. Fithri NA, Mardiyanto M, Novita RP, Andrean V. Furosemide self Nano emulsifying drug delivery system (SNEDDS)

formulation comprising of capryol-90, polysorbate-80, and peg-400 with simplex-lattice-design. STI. 2017;2(4):85-8. doi: 10.26554/sti.2017.2.4.85-8.

58. Pratiwi L, Fudholi A, Martien R, Pramono S. Self-nanoemulsifying drug delivery system (Snedds) for topical delivery of mangosteen peels (Garcinia mangostana L.,): formulation design and *in vitro* studies. J Young Pharm. 2017;9(3):341-6. doi: 10.5530/jyp.2017.9.68.
59. Murrukmihadi M. Optimasi formila sediaan sirup mukolitik *in vitro* fraksi terstandar bunga kembang sepatu (Hibiscus rosa-sinensis L.). Dr. Diss, Universitas Gadjah Mada; 2013. Available from: http://etd.repository.ugm.ac.id/home/detail_pencarian/57438.
60. Esim O, Savaser A, Ozkan CK, Bayrak Z, Tas C, Ozkan Y. Effect of polymer type on characteristics of buccal tablets using factorial design. Saudi Pharm J. 2018;26(1):53-63. doi: 10.1016/j.jsps.2017.10.013, PMID 29379333.