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Original Article

EXPLOITING THE DESIGN OF EXPERIMENTS FOR PREPARING EXTENDED-RELEASE DOSAGE FORM OF GLICLAZIDE USING THE HOT-MELT EXTRUSION TECHNIQUE

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ABSTRACT

Objective: Polyethylene Oxide (PEO) is an amphiphilic polymer available in various grades, allowing manipulation of drug release rates. This work hypothesized the attempt to combine Hot-Melt Extrusion (HME) and Design of Experiments (DoE) with mixtures of various PEO grades to efficiently produce a dosage form with tailored drug release.

Methods: MODDE software recommended sixteen runs. A D-optimal mixture design evaluated the effects of gliclazide, PEO 303, and PEO 205 on the release profile of extrudates containing, as well fixed amounts of Polyethylene Glycol (PEG) 8000 and Colloidal Silicon Dioxide (CSD). The formulations were extruded at a screw speed of 20 rpm using a vertical lab-scale single screw with four heating zones set at 85, 90, 90, and 95 °C. The most discriminative dissolution method was used to generate release profiles of extrudate containing 30 mg of the drug. Factors affecting the drug release rate at 1, 3, 4, and 6 h were identified and modeled.

Results: The goodness of fit (R^2) and prediction (Q^2) for release responses were 0.969 and 0.830 at 1 h, 0.983 and 0.760 at 3 h, 0.987 and 0.687 at 4 h, and 0.947 and 0.786 at 6 h, respectively. The optimal design space for PEO 303 as a release-retarding polymer and PEO 205 as a release modifier at each gliclazide level (10–30%) was successfully constructed by Response Surface Modeling (RSM).

Conclusion: This work produced an extended-release profile of gliclazide that mimics the innovator by leveraging HME and DoE.

Keywords: Gliclazide, Diamicron, Hot melt extrusion, Hydrophilic matrices, Polyethylene oxide, Design of experiments, Response surface methodology

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INTRODUCTION

The pharmaceutical industry has always strived to constantly elevate product quality, lower production costs, and accelerate the development of new medicines. Obviously, the old traditional 'one factor at a time' approach that is used to identify which factors have a real influence on the outcome is effortful and time-wasting. On the contrary, DoE is considered a superior approach that should be extensively implemented for formulation development [1–3]. Design of Experiments (DoE) is a systematic and organized approach in which all factors are simultaneously varied, which will allow allocating their relationships, interactions, and behaviors towards each other when combined at different levels and extents. The knowledge gained with the DoE guarantees developing of the optimum formulation that delivers the best product performance. Furthermore, DoE additionally enables the employment of response surface modeling in order to optimize the drug delivery systems via exploring the relationships between the selected variables and their responses using the least number of experiments [4–6].

Hot-melt Extrusion (HME) is a very well-tested pharmaceutical manufacturing technique, and its reliability has been proven over the last two decades [7]. It was primarily adopted as an efficient alternative to prepare solid dispersions/solutions of drugs [8, 9]. The purpose of such formulations is to overcome the extremely poor aqueous solubility of many of the newly discovered chemical entities. On the other hand, HME is an unconventional technique that has been shown through several proof-of-concept studies to hold great potential for preparing extended-release products [10-13].

Oral dosage forms are the most preferred by patients and of the easiest use. Modified-release dosage forms add extra advantages to this route of administration. They can offer uniform blood levels of the drug, which means more efficacy and fewer side effects [14]. They can delay or prolong the drug release to meet the therapeutic goals while ensuring better patient compliance [15, 16]. The aim of this study was to exploit and verify the validity of using the DoE in preparing an extended-release dosage form based on PEO as a polymeric carrier and the HME technique. Gliclazide, an orally administered antihyperglycemic agent, was chosen in this study as a model drug. By using DoE, we tried to identify and depict the margin of design space inside which the components of the mixture can be altered while preserving dissolution as a crucial quality aspect within the acceptable range and fairly verify that the model is both valid and applicable. Such a quality aspect should be ensured to serve the aim of mimicking the release profile of the innovator or to conform with the abridged acceptance criteria in order to guarantee bioequivalence.

MATERIALS AND METHODS

Materials

Gliclazide was graciously granted from Pharma International LTD (Amman, Jordan). PEO grades POLYOX WSR-205 and POLYOX WSR-303 were graciously provided by the Dow Chemical Company (MI, USA). Polyethylene glycol 8000 (PEG 8000) was purchased from ACROS Organics (NJ, USA). Colloidal silicon dioxide (CSD) was purchased from Cabot Corporation (MA, USA). Concentrated HCl was purchased from Lobachemie Pvt. Ltd. (Mumbai, India). Diamicron MR 30 tablets with lot number 06285108000136 were purchased from the local market.

Preparation of physical mixtures (PM)

The same routine was followed with all of the 16 experiments suggested by the DoE. The PM were prepared from different formulations containing different proportions of the active ingredient, PEO 205, and PEO 303. CSD was squandered and frittered in a polyethylene bag. PEG 8000 flakes were grinded with a mortar and pestle. The materials were precisely weighed individually and mixed manually together in a polyethylene bag for five minutes.

Preparation of extrudates

The prepared PM of each formulation were flood fed into the hopper of a lab-scale vertical single-screw Randcastle microtruder Model RCP-0375 which has a screw diameter of 0.3750 inches and a ratio

of the working length to diameter is 24 (Randcastle Extrusion Systems Inc., Cedar Grove, NJ, USA). The extrusion system is composed of three heating zones and a rod-shaped die with a diameter of 0.4 cm. The temperatures of which respectively are: 85 °C, 90 °C, 90 °C, and 95 °C. Such processing temperatures are well below the reported melting point of gliclazide is 169.1 °C [17]. The extrusion was processed at a speed of 20 rpm. The cylindrical extrudates were left to cool at room temperature for one day before they were manually cut into mini matrices with different weights and sizes, each corresponding to 30 mg gliclazide. The surface area of extrudates was not constant; it was rather an uncontrolled factor in this work.

Dissolution

The most discriminative dissolution medium was used in the assessment of the release profiles of the innovator Diamicron 30 and extrudates equivalent to 30 mg gliclazide each [18]. Briefly, 0.1 N HCL medium was prepared, and 900 ml were transferred to each dissolution vessel. After equilibrating the medium at a temperature of 37±0.5 °C, the dissolution experiments were started using apparatus I with a rotating speed of 100 rpm. Samples of 5 ml were aliquoted from the test fluid without medium compensation at predetermined time points for nine hours. The samples were passed through a 0.45-µm millipore filter and further analyzed at l = 290 nm using a UV-VIS single-beam spectrophotometer (Model 9200; United Kingdom). All measurements were performed in duplicates, and the amount of gliclazide released was determined using a respective calibration curve.

Design of experiments

In formulation of pharmaceuticals, the level of all components cannot be separately manipulated because they are dependent variables. There are always upper and lower bounds for each component in these mixtures. This will add restraints on the proportions of each of them, which can be optimized by DoE. Thus, a D-optimal design was applied for RSM in order to find out which combination of factors will produce extrudates with optimal release profiles of the model drug [19]. The plasticizer PEG 8000 and the glidant CSD levels were fixed at 20% and 1%, respectively. The other three factors that would affect the release of the model drug and their respective investigated levels were:

- Gliclazide level: 10%-30%
- POLYOX WSR-303 level: 0%-69%
- POLYOX WSR-205 level: 0%-49%

The release at 1, 3, 4, and 6 h were recorded for each formulation as the responses in the generated DoE based on the established acceptance criteria for gliclazide release over time from the innovator extended-release product. MODDE 11 software (MKS Data Analytics Solutions, UEMA, Sweden) was used to generate the experimental design with the objective of optimizing the G-efficiency of the design. The G-efficiency evaluates the performance of the design as compared to a fractional factorial one. The largest G-efficiency, the better is the design. Good designs have a G-efficiency of 50% or larger. The software suggested 16 experiments, including 4 center points, as shown in table 2. This gave a satisfactory G-efficiency of 71.76. Another evaluation criterion of D-optimal designs is the condition number. Good designs should have a condition number<8. The suggested design had a condition number of 4.925, indicating an acceptable design (MODDE 11 user guide).

Polynomial functions, including the factors, and their interaction terms were generated for all the release responses using Partial Least Square (PLS) fitting approach. The models' predictive ability/validity was evaluated based on the R^2/Q^2 diagnostics of the fit. Finally, contour plots were drawn to visualize the effect of various factors on the release of gliclazide at the specified time points.

RESULTS

Dissolution profile of Diamicron® 30

There is no official monograph for gliclazide extended-release tablets in the United States (USP) or the British pharmacopoeia. Nevertheless, the various compendia state that for extended-release products, a minimum of three-time points is required to set the dissolution specification. These time points should cover the early, middle, and late stages of the dissolution profile. The early time point is to exclude dose dumping, while the middle point is useful to ensure compliance with the shape of the dissolution profile. This middle time point is usually set where ~ 50% of the drug has been released. Finally, a late time point is required to ensure that the majority of the active substance has been released (>80% dissolved).

The dissolution test was performed for the innovator's Diamicron® 30 using apparatus I dissolution system. One Diamicron®30 tablet was placed in each basket of the apparatus that rotates at a speed of 100 rpm in a vessel containing 900 ml 0.1 N HCl of which the temperature was set at 37°C [18]. The release profile of Diamicron® 30 in this medium is plotted in fig. 1. This release profile is of utmost importance because it represents the therapeutically accepted release rate of gliclazide in this dissolution media regarding the innovator's plan.

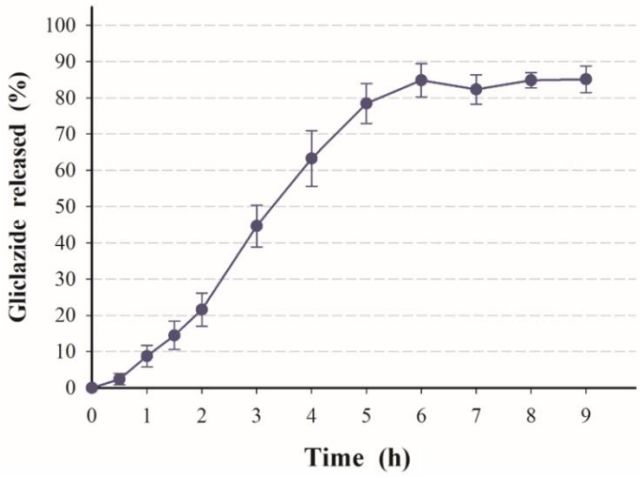

Fig. 1: The release profile of the innovator's Diamicron® 30 in apparatus I dissolution system. Each point represents the average release of 6 Diamicron®30 tablets

Based on the innovator release profile in this discriminative dissolution medium, dissolution acceptance criteria were suggested as summarized in table 1. To better resemble the release of the innovator product, an extra middle time point was included in the suggested acceptance criteria. It is generally recommended that the range at any dissolution time point specification is within±10%

deviation from the mean dissolution profile obtained from the innovator. Therefore, the acceptable percentage of gliclazide released at each time point was based on ±10% deviation of the average release of gliclazide from Diamicron®30.

Table 1: Suggested dissolution acceptance criteria for gliclazide release over time from extended-release preparations

Time (h)	Amount dissolved
1	between 5% and 18%
3	between 35% and 55%
4	between 53% and 73%
6	not less than 80%

Preparation of extrudates

The hydrophilic polymer PEO with a molecular weight of 7000000 (POLYOX WSR-303) was chosen as the matrix former to prolong the release of the model drug gliclazide. As a release modifier, the same polymer but with a lower molecular weight was selected. PEO with a molecular weight of 600000 (POLYOX WSR-205) was considered a suitable, extrudable, and compatible release modifier for processing alongside POLYOX WSR-303 by HME at the condition specified previously.

In order to set the upper and lower bounds of factors that influence the release of the model drug, preliminary trials were conducted to establish the processing requirements to enable extrusion of gliclazide formulations. Initially, a formulation of 69% POLYOX WSR-303 with gliclazide loading at 10% level and 20% of PEG as a plasticizer was prepared. However, the poor flowability of this formulation rendered it non-extrudable due to the insufficient powder screw feeding. In order to resolve this issue, 1% CSD was incorporated as a glidant. It was noticed that the powder mix showed remarkable improvement in flowability after the incorporation of the glidant into the mixture, and now it could be efficiently fed to the extruder.

A successful extrusion of this formulation was achieved without any system overload as the pressure capacity of the device was not exceeded. The melt pressure was always below the limit of 4000 Pound-force per Square Inch (PSI) set by the manufacturer. Extrudates were collected and cut into pieces corresponding to 30 mg of gliclazide. The release profile of these extrudates is presented in fig. 2 (designated as DoE experiment # 1). A very slow release was obtained from this formulation, with a release of only 75.84% after 10 h. Similarly, a formulation comprising the same level of plasticizer and glidant was prepared but incorporating gliclazide at 30% with the release modifier only (POLYOX WSR-205) at 49%. Almost a complete release of 90% of gliclazide was evident in as short as 3 h from starting the dissolution experiment (fig. 2, designated as DoE experiment # 2).

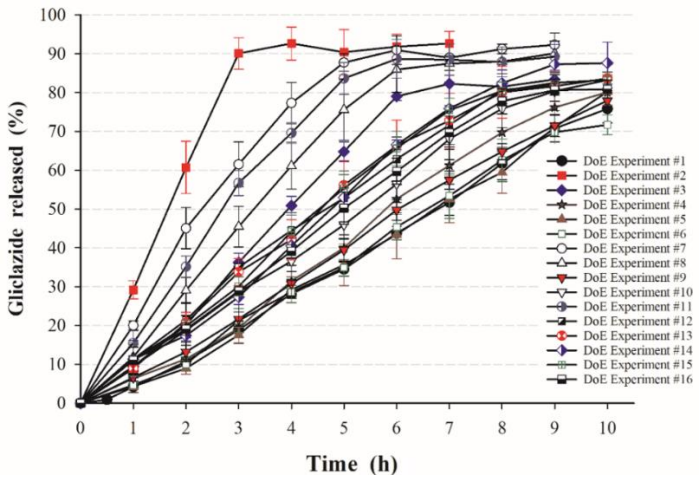

Fig. 2: The dissolution profiles from extrudates of 16 experiments suggested by the DoE software. Each point represents the average release of 6 extrudate pieces corresponding to 30 mg gliclazide each

After these preliminary formulation optimization trials, the boundaries within which the formulation factors in the mixture design ought to be varied were identified (table 2). Moreover, the required amounts of plasticizer and glidants to carry out a successful extrusion of the powder mix within the proposed mixture design were set. All the subsequent formulations suggested by the DoE software showed excellent flowability and extrudability by incorporating 1% CSD and 20% PEG 8000, respectively.

Table 2: The effect of mixture composition on release responses of gliclazide at 1, 3, 4, and 6 h

Experiment number	Polyox 303 %	Polyox 205 %	Gliclazide %	Release % at 1 h	Release % at 3 h	Release % at 4 h	Release % at 6 h
#1	69	0	10	4.22	18.85	28.17	43.80
#2	0	49	30	29.18	90.09	92.66	90.41
#3	20	49	10	9.48	36.238	50.918	79.03
#4	49	0	30	6.35	19.29	31.49	52.63
#5	62.3333	0	16.6667	4.30	17.57	29.20	43.47
#6	55.6667	0	23.3333	4.67	21.29	28.62	45.40
#7	6.66667	49	23.3333	20.09	61.54	77.30	90.96
#8	13.3333	49	16.6667	11.86	45.49	61.16	85.964
#9	52.6667	16.3333	10	6.61	21.64	30.75	49.80
#10	36.3333	32.6667	10	9.52	28.61	36.57	56.47
#11	16.3333	32.6667	30	15.46	56.74	69.58	88.68
#12	32.6667	16.3333	30	11.35	34.99	44.53	62.87
#13	34.5	24.5	20	8.93	33.76	42.13	66.33
#14	34.5	24.5	20	11.31	27.36	40.50	66.56
#15	34.5	24.5	20	11.27	30.10	44.19	65.63
#16	34.5	24.5	20	11.07	28.91	39.11	59.73

Dissolution testing

Fig. 2 presents the dissolution profiles from extrudates prepared according to the mixtures suggested by the DoE software and processed under the same conditions. As a general notice, the dissolution medium was, as expected, highly discriminative and able to detect differences in the composition of the formulations in terms of the percentage released of gliclazide.

As mentioned previously, DoE experiment #1 was set as the lower boundary and is anticipated to result in the slowest release rate of gliclazide. In this experiment, the formulation comprised gliclazide at the lowest level screened in this work, which is 10% as well as PEO 303 as a matrix former and release retardant at the highest level of 69%. No PEO 205 as a release modifier was incorporated in this formulation.

The other formulations that did not incorporate the release modifier are DoE experiments #4, 5, and 6. The level of gliclazide was increased in these experiments on the expense of PEO 303 level to 16.66%, 23.33%, and 30% in DoE experiments #5, 6, and 4, respectively. The release profiles of DoE experiments #5 and 6 were similar to those of DoE experiment # 1 in spite of sacrificing PEO 303 for increasing the level of gliclazide. In DoE experiment #4, a further increase of gliclazide level to 30% was implemented. Interestingly, this further increase in gliclazide level did not elicit any noticeable increase in the release rate till the elapse of four hours of the dissolution experiment. From visual inspection, it was noticed that the gelling, swelling, and erosion of these four experiments were similar. Apparently, the release of gliclazide is controlled by the gelling and slow erosion of the matrix former PEO 303. Nevertheless, it is expected that increasing drug level at the expense of the release retarding polymer should result in increased porosity after dissolution of the drug that potentially will cause a further increase in the release rate with time. However, this was only observed upon incorporation of >23.33% of gliclazide. The drug to polymer ratio in these systems appears to be of crucial importance because this ratio has a very decisive effect on the release rate of the drug [20].

With regard to the effect of inclusion of the release modifier PEO 205, consider DoE experiments # 3, 9, and 10 in which the percentage of PEO 205 was 49%, 16.33%, and 32.6%, respectively. The percentage of gliclazide was fixed at 10% in all three experiments as, similar as to DoE experiment # 1. DoE experiment #10 showed a relatively faster release rate compared to DoE experiment # 9. After six hours, approximately 56.5% of gliclazide was released from DoE experiment # 10 as compared to only 49.8% release after the same time in DoE experiment # 9. This is easily explainable because in DoE experiment #10 the percentage of the lower molecular weight PEO 205 was doubled at the expense of PEO 303 compared to DoE experiment # 9. In DoE experiment #3, the level of the release modifier was further increased to 49% and the level of PEO 303 was reduced to 20%. This significantly boosted the release rate of the model drug resulting in 79% release after 6 h of dissolution.

The same behavior was obtained in DoE experiments #11 and 12. The level of gliclazide in these two experiments was fixed at 30%. On the other hand, the level of release modifier was increased from 16.33% in DoE experiment # 12 to 32.33% in DoE experiment # 11. There was ~ 26% increase in the percentage of drug released after six hours in DoE #11 as compared to DoE experiment # 12. This is in line with the expectation attributed to the characteristics of both grades of the PEO polymers.

The projected general effects for varying the mixture design are also supported by comparison of DoE experiments #2, 3, 7, and 8. Here, the level of the release modifier PEO 205 was fixed at the maximum level, which is 49%. Contrary wise, the level of the drug has been changed ascending in the following order 3, 8, 7, and 2. Accordingly, the release of the drug increased following the same order. In addition to the effect of increasing the drug, the enhancement in release is also attributed to the gradual decrease of the level of the release-retarding polymer from 20% in DoE experiment #3 to 13.33%, 6.67%, and 0% in DoE experiments #8, 7, and 2, respectively.

An extremely interesting observation was perceived upon comparing the release profiles of DoE experiments #10 and 12. In DoE experiment number 10, the level of gliclazide was 10% and that of the release modifier PEO 205 was 32.67%. In DoE experiment #12, the level of the drug was increased to 30% mainly on the expense of the release modifier, which was reduced by half to 16.33%. In spite of this significant drop in the percentage of incorporated release modifier, gliclazide release in experiment #12 was unusually faster than that of DoE experiment # 10. Such behavior announces that the percentage of the drug has a profound effect on the release rate as that of the release modifier. Increasing the percentage of gliclazide to 30% in DoE experiment # 12 appears to counteract and supersede the effect of decreasing the release modifier.

A higher percentage of drug in the formulations means a lower percentage of polymers, which will result in lots of voids and spaces upon drug release that can result in a much faster release rate. A higher percentage of drug can also affect the thickness and formation time of the gel layer responsible for the modified release of the drug. This obviously highlights our approach of exploiting DoE to vary the factors simultaneously in order to determine and quantify the factors' individual effects as well as their interaction.

Finally, the dissolution profiles of the four center points were also recorded. The four dissolution profiles overlap and intersect in many regions, indicating a similar release rate. It should be emphasized that these experiments were performed on different days according to the random run order suggested by the software. This points out that the whole process of powder mixture preparation and processing as well as the subsequent dissolution and analysis were highly reliable and reproducible.

Response surface analysis

RSM is a set of mathematical and statistical techniques that can be expressed by the following general equation:

$$y = f(x_1, x_2, \ldots x_n) + e$$

Where y is the response variable, which is a dependent one, x_1, x_2 and x_n are the independent variables (factors). The dependent variable is a function of the independent ones. The experimental error term is denoted as *e*, which represents any measurement error on the response as well as other types of variations not counted in *f*. In RSM, the true response function (*f*) most of the time is unknown. In order for RSM to suggest a useful experimental design, an approximation to the response function *f* should be known.

In this research, the first two experiments that resemble the suggested upper and lower limits of response attributed to the properties of both PEO grades helped giving a good approximation to the response function. According to which, a complete experimental design set of 16 experiments with four center points was proposed by software. The responses in terms of the percentage released of gliclazide at 1, 3, 4, and 6 h for each of these suggested experiments are summarized in table 2.

Utilizing PLS fitting approach, the release responses data at different times gathered from the 16 experiments were used to develop mathematical models in the form of second-order polynomial equations. In order to improve the initial mathematical models in terms of R^2 and Q^2, transformation of the responses was investigated. The best modelling was obtained upon logarithmic transformation of the first two responses only, while the other responses were kept as such. Consequently, the following two equations were generated.

For the release at 1 and 3 h

$$\text{Log}(Y) = a_{0+}(a_1{*}\ \text{PEO 303}) + a_2{*}\ \text{POLYOX-205} + a_3{*}\text{gliclazide} + a_{11}{*}(\text{POLYOX-303})^2 + a_{22}{*}(\text{POLYOX-205})^2 + a_{33}{*}\ (\text{gliclazide})^2 + a_{12}{*}\text{POLYOX-303}{*}\text{POLYOX-205} + a_{13}{*}\text{POLYOX-303}{*}\text{gliclazide} + a_{23}\ {*}\text{POLYOX-205}{*}\text{gliclazide}$$

For the release at 4 and 6 h

$$Y = a_0 + a_1\ {*}\ \text{POLYOX-303} + a_2{*}\ \text{POLYOX-205} + a_3\ {*}\ \text{gliclazide} + a_{11}{*}(\text{POLYOX-303})^2 + a_{22}\ {*}\ (\text{POLYOX-205})^2 + a_{33}\ {*}\ (\text{gliclazide})^2 + a_{12}\ {*}$$

POLYOX-303 x POLYOX-205+a_{13} * EC * gliclazide+a_{23} * POLYOX-205 * gliclazide

Where,

Y: is the percentage of gliclazide releases.

a_0, a_1, a_2, a_3, a_{22}, a_{33}, a_{12}, a_{13} and a_{23}: are the release rate coefficients of multiple components.

Table 3 summarizes R^2 parameters quantitatively regarding the response values in terms of the percentage release of gliclazide at the four-time points. The model is highly valid as all the values lie higher than the acceptable model validity of 0.25. R-squared is simply defined as the percentage of the response variable variation explained by the model. The more the value of R-squared is close to 100%, the more the model is able to explain the variance of the response around its mean. In other words, it means the more the response variable, which is gliclazide release at a specific time point, is affected and dependent on the independent variables. From the values of R^2 and Q^2, one can also deduce how close the data collected are to the values predicted by the model. And that explains how acceptable R^2 is. Generally, if the differences between the observed values and the model's predicted ones are small and unbiased, then the model fits the data very well.

Table 3: Goodness of fit parameters

Response	R^2	Q^2	Model validity	Reproducibility	p-value* (Regression)	p-value** (Lack of fit)
Release at 1 h	0.969	0.830	0.843	0.954	0.000	**0.535**
Release at 3 h	0.983	0.760	0.929	0.963	0.000	**0.753**
Release at 4 h	0.987	0.689	0.774	0.987	0.000	**0.407**
Release at 6 h	0.947	0.786	0.631	0.963	0.000	**0.229**

R^2: goodness of fit, Q^2: goodness of prediction, *: indicates a significant regression model when P<0.05, **: indicates lack of fit of the model when P<0.05

At all four time points, there was no lack of fit as the p-values are higher than 0.05. On the other hand, the p-values of regression for the four models are below 0.05. This clearly designates a significant association between predictor variables and the response variable; which indicates a significant regression model in which the predictor variables are meaningful additions to the model and are highly sensitive to change that is readily attributed in the response variable; the release rate of gliclazide in this case. Finally, this model shows high reproducibility, which implicates how precise and accurate the whole process was. In conclusion, the current findings show that the four generated models are valid, reproducible, precise, accurate, and most importantly, they fit the data very well.

Regression coefficient plots

The regression coefficient plots in fig. 3 represent the distribution of the individual effect of each predictor variable as well as their interactions on the response variable during the entire six hours. In the regression coefficient plot for modeled gliclazide release at the first hour, important information can be debriefed. First, the release retardant effect of PEO 303. This obviously explains how adding a percentage of the mentioned polymer grade can slow down the release rate of gliclazide significantly. On the other hand, the release-enhancing effect of PEO 205 and Active Pharmaceutical Ingredient (API) shown in the second point and third point, respectively, confirms what was previously illustrated in the dissolution section about how the added percentage of each of PEO 205 and API can readily enhance the release rate of the drug. However, the last point on the right shows that the interaction effects on the release rate are lower than those of the individual effects of each factor. The individual effect of any predictor variable on the regression coefficient plot stands on the idea that all the other variables are constant in the meantime. Apparently, from fig. 3, the most influencing effects on the release of gliclazide are those derived from the individual predictor variables rather than their interactions.

In the other regression coefficient plots for the release of gliclazide at 3, 4, and 6 h, the same general trend is observed. This indicates that the effect of each predictor variable on the response variable proceeds almost statically during the whole six hours. With time, however, the net effect of combined variables approaches zero. In the final plot, one can barely notice a net effect of any combination. As most of the matrix has been eroded near the end of the release experiment, it is not the combination that can explain the release behavior of the system rather than the individual percentage of each predictor variable.

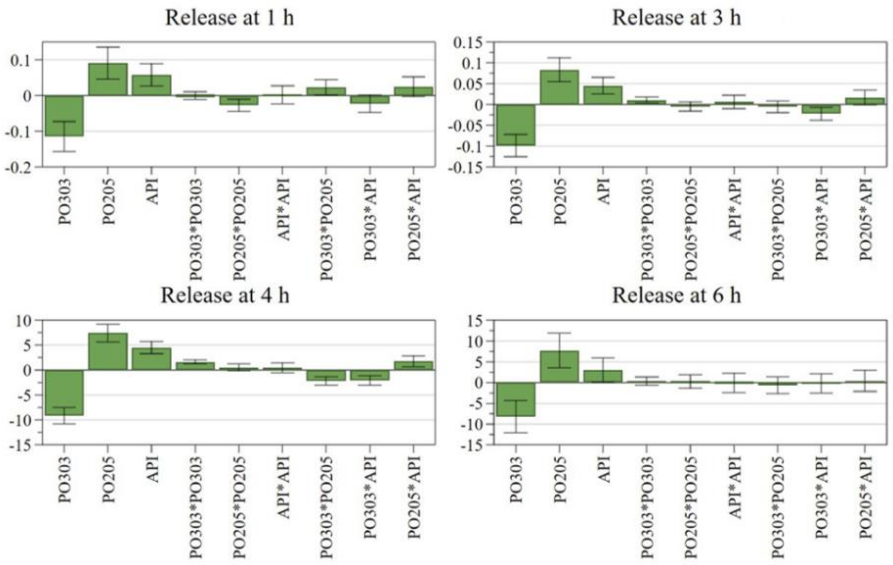

Fig. 3: Regression coefficient plot. Each bar represents the mean individual effect of each predictor variable on the response variable

Ternary contour plots

The ternary contour plots are considered barycentric plots on three variables, which should sum to a constant. Since PEO 303, PEO 205, and gliclazide are the main three predictor variables that affect the response variable; their sum constant should be 79 %, since this is the added concentration of all of them in every single experiment, leaving a 21% for PEG and CSD respectively.

Each of the four plots in fig. 4 presents the influence of different mixture compositions on the percentage of gliclazide released at a time point. These ternary contour plots are especially important to study the relationships between different predictor variables and their sum effect on the percentage released of gliclazide. To understand such a relationship, the area of focus should be centered on one thing only: how response changes according to different compositions and why. Exposition of all the above information on contour plots will be briefly performed in the following paragraphs.

The first ternary contour plot presents the effect of different compositions of the three predictor variables on the percentage release of gliclazide at the first hour. Paying attention to the coloured area in the graph, one can understand how crucial the percentage of gliclazide is to the effect exerted by the composition on the response variable. It should be kept in mind that the response variable is nothing but the percentage release of gliclazide itself. To illustrate, let us consider the point where gliclazide percentage is exactly equal to 0.1. Regardless of the concentration of the other two components, the percentage released of the drug is always less than 10% in the first hour. However, as the level of gliclazide in the composition is increased, an increased margin of possibilities arises with it in terms of the percentage of drug released in the first hour. For instance, at the point where gliclazide percentage is between 20% and 30%, a higher percentage released of the drug can be achieved after the first hour, especially with a lower percentage of PEO 303 on the left.

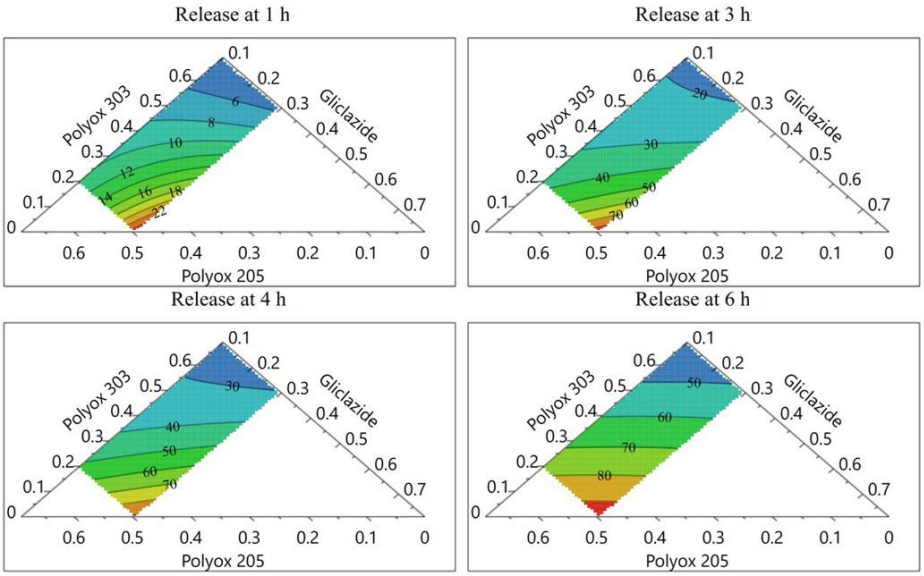

Fig. 4: Contour plots illustrating the influence of the mixture composition on the amount of gliclazide released at various time points

The second plot in fig. 4 for the release at 3 h clarifies things even more. It is obvious that moving down the ternary plot, which means a lower level of PEO 303, gives a better chance of a higher percentage release of the drug. The higher release is more profound in compositions that incorporate higher levels of gliclazide. In this plot, the percentage of drug released after three hours at a certain point within the crayon-colored area actually meets the acceptance release criteria i. e., between 35% and 55%. The composition at this point is about 30% of each PEO 303 and PEO 205, and a 20% of gliclazide. However, this composition cannot be considered an optimum composition to produce the final product that would mimic the innovator's release acceptance criteria. To be so, this composition must also meet the release acceptance criteria at the other time points as well. Moreover, it is not the aim of this project to define a single composition that meets the innovator's release rather than to define the range of compositions that would fulfil that purpose. For instance, the same spot mentioned above could not meet the acceptance release at four hours, as can be illustrated from the third ternary contour for the release at 4 h.

In the last two plots, the contour lines are getting more linear and less curvy. This indicates that after four hours, the release rate of the drug starts to get more static depending on the actual composition of the formula. In the contour plot, which presents the effect of mixture compositions on the percentage released of gliclazide after six hours, it can be easily noticed how contour areas are separated by straight lines between which lies the final percentage released of gliclazide. Perhaps this is why the release at four and six hours could be modelled acceptably without the need for any mathematical transformation as that required for the release at the first two time points.

In the current work, the experiments already performed cover the experimental space illustrated by the colored areas in the contour plots. But what about mixture compositions outside of this experimental space (represented by the white areas in the figures)? This study was intended to investigate the ability of HME to produce a sustained-release gliclazide product that meets certain release criteria utilizing DoE. Once this goal is achieved, there should be no need for further experiments outside the current experimental space. For instance, if the empty area on the right side of each ternary plot was intended to be investigated, it would mean having formulations that incorporate higher levels of gliclazide than 30%. However, higher levels of the drug will be subtracted from the percentage of matrix-forming polymer. This will in turn be reflected by a lower chance of a well-controlled drug release, which would fail the main aim of the study. In addition, the ternary plot reveals that at such higher levels of the drug, the percentage released will be a lot higher than needed to mimic the innovator's.

Optimization

One of the supreme aims of this work was to use RSM to generate a design space within which the formulation factors that affect the dissolution profile gliclazide can be varied and still meet the requirements of innovator's release profile. Graphical optimization by the MODDE software was fruitfully employed to divide the

experimental space into district regions according to the number of constraints that have been fulfilled (fig. 5). The optimal area (sweet spot) in red represents the composition within which the mixture of the three factors can be varied while meeting the innovator's release rate acceptance criteria. It can be inferred from the optimization plot that there is an optimum range of PEO 303 (10%-14%) that is necessary to be incorporated in order to achieve the innovator's release rate acceptance criteria. Likewise, the optimal area accurately gives the optimum range of each of the two other factors, namely gliclazide and PEO 205.

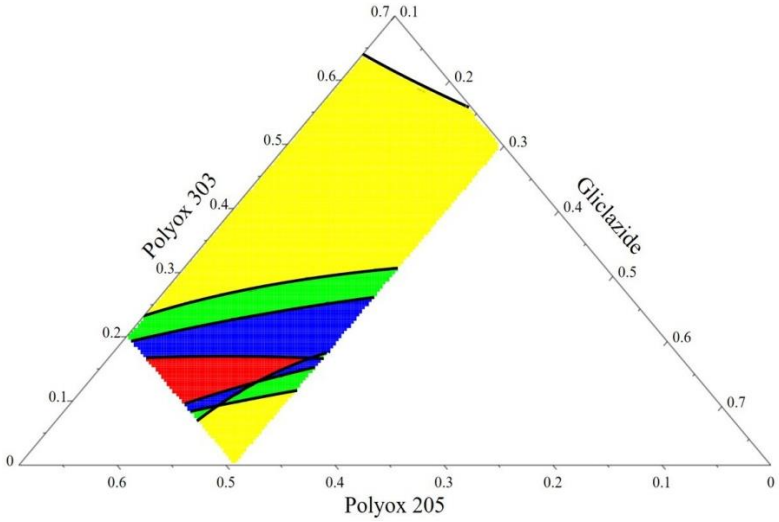

Fig. 5: Optimal area plots at various factor combinations. The optimal area is shown in red. Blue areas indicate the experimental space where one of the constraints is unmet. The green areas indicate the experimental space where two of the constraints are unmet. The yellow areas indicate the experimental space where three of the constraints are unmet. The white area indicates the experimental space where none of the constraints are unmet

Verification of the model validity

For the verification of the model validity and applicability, a specific composition was selected based on the graphical optimization executed on the design space. This composition comprised the following mixture:

- Gliclazide level: 20%
- POLYOX WSR-303 level: 14%
- POLYOX WSR-205 level: 45%
- PEG: 20%
- CSD: 1%

The above formulation was prepared, extruded, and processed under the exact same conditions under which the experimental design was processed. The release of gliclazide from this formulation was compared to the predicted response value summarized in table 4. This comparison showed that the practical release values of this sweet spot extrudate at the four-time points were within the predicted values. All the practical release values of the sweet spot verification were comparable to the predicted mean values at the four-time points. This fairly verifies that the model is both valid and applicable.

Table 4: Predicted release (%) versus observed release (%) of gliclazide from extrudates prepared at the verification checkpoint

Response	Predicted release	Lower limit	Upper limit	Experimental result*
At 1 h	14.83	13.06	16.83	14.8±3.32
At 3 h	48.61	44.82	52.73	51.69±4.16
At 4 h	63.96	61.22	66.71	65.05±4.32
At 6 h	82.72	77.54	87.90	83.27±3.18

*: mean Release from 6 extrudates pieces corresponding to 30 mg gliclazide each±standard deviation.

DISCUSSION

Polyethylene oxide-based matrices for sustaining the release of drugs have been prepared by several manufacturing techniques, such as compression-molding [21], direct compression [22, 23], and HME [24-26]. Various grades of low and high molecular weight as well as their blends, were investigated with and without additives and using varying levels of drug loading. It appears that the drug release from PEO matrices is a complex process that is affected by several factors, such as the molecular weight of the PEO used, manufacturing method, the presence of additives, and the drug loading percentage [21-28]. The most important factor among these is the molecular weight of PEO. There is a shift in the mechanism of release from the relatively rapid and constant swelling/erosion in case of low molecular weight PEO to a slow and non-constant anomalous release kinetics governed by the swelling of the high molecular weight grades.

Using a mixture of different grades of PEO can offer great flexibility in accomplishing the needed release profile [29, 30]. The high molecular weight of this carrier would act as a release-retardant carrier. On the other hand, lower molecular weight grades can help to increase the release of the drug. Accordingly, two polymer grades of POLYOX were used, namely, PEO 303 and PEO 205. To this end, the central objective of this work was to exploit the DoE to deconvolute the aforementioned complexity of PEO-based matrices in terms of drug release and to establish an extended-release delivery system of the model drug gliclazide using HME as the principal manufacturing technique. The levels of the plasticizer PEG 8000 and the glidant CSD were fixed at 20% and 1%, respectively. The other three constituents of the

formulations were considered the main factors that can adjust the release rate of the model drug, gliclazide. These independent variables namely are PEO 303, PEO 205, and gliclazide itself. The mathematical models were developed in hope of statistically expressing and analyzing the results to quantitatively express the effects of these independent variables on the response variable, being the release rate of the drug at 1, 3, 4, and 6 h.

The most fundamental outcome in this study was establishing mathematical models according to which the dissolution results were analyzed and presented and proven valid and sound, as explained throughout R^2 parameters presented in table 3. These satisfactory polynomial models for forecasting the effect of the mixture composition on the release rate of gliclazide were generated with sufficient reliability. They are centered on the three factors scrutinized on top of their interactions and their concerted effect on the release rate of the drug. Furthermore, these models were used to craft the ternary contour plots to facilitate the graphical visualization of the effect of varying mixture compositions on the release responses.

Finally, we were able to use these mathematical models to define the margin of design space inside which the components of the mixture can be altered whilst preserving the crucial quality aspects within the acceptable range. Those quality aspects are designed to serve the aim of mimicking the release profile of the innovator or to conform with the abridged acceptance criteria in order to guarantee bioequivalence. DoE has been proven in this work to serve as a robust utensil in that purpose, as it grants the ability of graphically identifying and optimizing the operational range that simulates the encoded set of constraints. Regarding the extended-release gliclazide, those constraints are based on the release profile of the originator specified in Diamicron since a monograph for the gliclazide extended-release tablet is not available.

With regard to the use of gliclazide as a model drug, it is a good candidate for the purpose of this study due to its availability in the market in a sustained-release dosage form. In addition, its relatively low dose is essential for formulating such dosage forms through HME. The melting point of Gliclazide and maximum extrusion temperature were 169.1 and 95 °C, respectively. Although partial solubilization of the model drug in the molten mixture cannot be excluded, the relatively high melting point of the model drug as compared to the extrusion temperatures, assures that the majority of the drug would retain its crystallinity after extrusion. Therefore, no confirmatory experiments, such as powder X-ray diffraction, were performed to illustrate the obvious.

PEO can be highly viscous when melted during the processing by extrusion. Increasing the processing temperature with the aim of reducing viscosity is not a rational choice. Processing at a relatively high temperature has been shown to cause degradation and chain scission of POLYOX [25]. Moreover, degradation of the drug can occur. Plasticizers can be highly helpful in this case. Thus, PEG 8000 was used at a 20% level to help in extrusion of POLYOX mixtures without exceeding the pressure and torque confines of the extruder. One of the advantages of using the solid-state plasticizer PEG 8000 in HME is that there is no transition into the crystalline state during the HME process. PEG tends to dissolve in the polymer during the melting process yet stays in an amorphous form after cooling [31]. Without the use of the PEG 8000 as a plasticizer, the experiments may yield erratic viscosities of the melt, which in turn will lead to sporadic extrudate output in terms of extrudate quality, uniformity, and homogeneity. Moreover, PEG was advantageous in this work because it has great miscibility with PEOs which will allow it to embed itself within the polymer chains. Another criterion that should not be overlooked is that PEG has a pore-forming ability which will decrease the release-retardant activity of our carrier, complementary to the effect expected from the low-grade PEO release modifier.

CONCLUSION

This work succeeded in producing an extended-release profile of gliclazide that mimics that of the innovator by using HME as the principal manufacturing technique and DoE as an advanced combinatorial approach. The DoE helped proceed briskly and accurately in pursuing the aims of this study of which the most inclusive was finding the optimum conditions and levels of variables that succeeded in producing the targeted release profile of gliclazide using the HME technique. The use of different proportions of two different grades of PEO not only can yield different release profiles of the drug candidate at hand but also could ameliorate the process to what is advantageous and to finely tailor it to make it API specific. Although this work suggests using two grades of PEO for making a sustained release profile similar to the innovator, it stays specific to gliclazide used as a model drug in this work. The polymeric combination with HME resulted in a product whose release was shown to be governed by the properties of the active ingredient to a very decisive level.

FUNDING

Nil

ABBREVIATIONS

API; Active pharmaceutical ingredient; CSD, Colloidal silicon dioxide; DoE, Design of experiments; HME, Hot-melt extrusion; PEG, Polyethylene glycol; PEO, Polyethylene oxide; PLS, partial least square; PM, Physical mixture; PSI, Pound-force per square inch; Q^2, Goodness of prediction coefficient; R^2, Goodness of fit (coefficient of determination); RPM, Revolutions per minute; RSM; Response surface modeling; USP, United States Pharmacopeia.

AUTHORS CONTRIBUTIONS

Ibrahim Hashim: Data curation, investigation, analysis, and interpretation of results. Alia Kh. AlSuwais: Writing – original draft preparation. Alaa Abu Alhaija: Writing – review and editing. Ahmad Aljaberi: Conceptualization, methodology, interpretation of results, and draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

CONFLICT OF INTERESTS

Declared none

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