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Metformin HCl Controlled-Release Microparticles: DoE-Based Formulation Development and *In-Vivo* Proof of Concept Study

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ABSTRACT

Conventional drug delivery systems deal with side effects due to drug plasma level fluctuations. However, high dose or bulky formulations are a big issue for controlled drug delivery systems. In addition, burst release due to the cracking system exacerbates the rapid release and reduces the shelf-life. A controlled-release-based microparticle formulation is proposed to address this issue. This research aimed to develop and optimize controlled-release microparticles containing metformin HCl as a drug model and a mixture of Eudragit RS and Kollidon SR as a polymeric matrix using a Box-Behnken design, followed by in-vivo efficacy evaluation. Several characterizations were applied, namely, drug loading, entrapment efficiency, and particle size, to determine the optimized formulation. Metformin HCl concentration and drug-polymer ratio dominantly increased the particle size, drug loading, entrapment efficiency, and particle size variation. Optimized formulation produced a particle size of 1.363±0.03 µm and a narrow particle size distribution. Moreover, in-vitro evaluation showed that the release of metformin HCl microparticles followed Weibull kinetics. Moreover, the in vivo evaluation confirmed the ability of microparticles to control blood glucose levels in rats for up to 24 hours, along with a 59% reduction compared to a control group administered a conventional tablet formulation. The microparticle effectively controlled the drug release and reduced blood glucose levels in rats.

Keywords: controlled drug delivery system, microparticles, optimization

INTRODUCTION

Conventional drug delivery systems can fail to achieve therapeutic effectiveness due to fluctuations of plasma level and poor drug bioavailability (Adepu & Ramakrishna, 2021). Moreover, a fluctuating drug plasma level tends to induce toxic effects, mainly when the drug concentration is above the maximum toxic concentration due to the topping effect. Therefore, a controlled-release drug delivery system becomes the primary strategy to combat these limitations (Adepu & Ramakrishna, 2021). A formulation providing a controlled drug delivery system has a longer duration of action since the drug release was sustained for a certain period, thus minimizing the equal efficacy or toxic peaks and non-efficacy periods of a drug due to relatively constant plasma levels (Park et al., 2022). In addition, it enhances patient adherence by simplifying the daily dosing regimen (Baryakova et al., 2023).

A sustained release drug delivery system is commonly formulated with many excipients to form a matrix or layered coating structure (Singh et al., 2021). However, applying the system in conventional dosage forms like tablets, has certain limitations. Use of numerous excipients results in a dramatically larger dosage form that can be hard to swallow, so people often break a tablet into small pieces to obtain a size easier to swallow (Thong et al., 2018). However, to prevent dose dumping, a dosage form containing a sustained release drug delivery system should not be crushed (Gracia-Vásquez et al., 2017). Loss of formulation integrity has been reported to cause an extremely high drug dissolution rate, called burst release, as the matrix structure fails to control the drug dissolution

(Choiri et al., 2019). For this reason, a breakable formulation that obviates the issues of burst release and bulkiness of dosage form should be considered. Microparticles are promising candidates for formulating a sustained release delivery system for highly hydrophilic drugs in bulky dosage forms. Such formulations aim to avoid burst release effects with a breakable feature for easier dose administration.

Polymer-based microparticles are widely used as sustained release drug carriers (Sung & Kim, 2020). Freely water-soluble drugs with high drug loading require special features of the polymer matrix. Insoluble and swellable polymers are the best choice for active pharmaceutical ingredients. On the one hand, Kollidon SR is a co-processed polymer combining polyvinylpyrrolidone and insoluble polyvinyl acetate that presents channels when introduced into an aqueous medium. On the other, Eudragit RS, a copolymer of acrylate and methacrylate containing ammonium salts, is an insoluble but swellable polymer. The combination of Kollidon SR and Eudragit RS is proposed to provide a swelling matrix with channels as a drug release-controlling structure (Öztürk et al., 2017). The Eudragit RS-Kollidon SR mixture is reported to be capable of improving the mechanical robustness of a hydroxypropyl methylcellulose (HPMC) matrix and enhancing the ability to retard drug release (Choiri et al., 2019).

Metformin, applied as first-line therapy for type 2 diabetes mellitus, was selected as a model because the formulation of controlled delivery systems with this drug is a challenge due to its high drug loading and hydrophilicity. Metformin HCl sustained release microparticles using a poly(lactic acid) matrix were shown to retard drug release up to 24 h (Bouriche et al., 2021). Sustained release mucoadhesive microspheres containing metformin HCl with Eudragit RS as a matrix structure showed an antihyperglycemic effect for six hours (Kotha et al., 2023). Meanwhile, metformin HCl sustained release microspheres using a xanthan gum matrix slowed drug release for six hours (Yahoum et al., 2023). To the best of our knowledge, there are no reports describing Kollidon SR and Eudragit RS for microparticle-based sustained release metformin HCl. Therefore, this work aimed to formulate and optimize a microparticle-based sustained release drug delivery system for freely water-soluble drugs with high loading, and *in vivo* efficacy was evaluated in a proof-of-concept study.

MATERIALS AND METHODS

Eudragit RS and Kollidon SR polymers were obtained from Evonik (Essen, Germany) and BASF (Ludwigshafen, Germany). Dichloromethane, sodium dihydrogen phosphate, Tween 80, and sodium hydroxide were purchased from Merck (Darmstadt, Germany). Ultrapure destilated water was produced by Mili-Q system (Merck, Darmstadt, Germany). Alloxan (Sigma Aldrich; St. Louis, MO) was purchased from a local supplier. Metformin HCl (Sohan; Maraharastara, India) was obtained from PT Phapros as a gift sample.

Experimental design of microparticle formulation

The design and development of microparticle formulation were performed using a box-Behnken design. A 17-run was constructed according to the percentage of the drug in the system, drug-to-polymer ratio, and Kollidon SR concentration. The critical material attributes in this experiment consisted of drug-to-polymer ratio (1-2%), percentage of metformin HCl in the system (33-67%), and percentage of Kollidon SR (33-67%). The optimized formulation of microparticles was obtained with preferable size, entrapment efficiency, drug loading, and particle size distribution. A three-dimensional response surface plot was constructed to study the interaction effects of two independent variables on the responses while holding the third factor at a constant level.

Preparation of microparticles

An emulsion evaporation technique was applied to prepare the microparticle. Firstly, Kollidon SR and Eudragit RS polymers were dissolved separately in 2.5 mL methanol; the drug was dissolved in 5.0 mL. In addition, the mixture was sonicated using a DSA50 ultrasonic bath (Fuzhou, China) for 15 min at 25°C. The polymer mixture and drug solution were added to 2.5 and 5.0 mL dichloromethane. The three mixtures were sonicated separately for 15 min at 25°C until a clear solution was achieved. The oil phase was obtained by mixing polymers and drug solutions.

Emulsification was accomplished by adding the oil phase to the water phase mixture and 2% Tween 80 as a surfactant to form a microemulsion. The emulsification was performed using an IKA T25 Digital Ultra-Turrax (Staufen, Germany) at a rotation speed of 7000 rpm for 10 min. Furthermore, the solvent was evaporated under stirring (600 rpm) at ambient conditions (27±2°C, RH 60±5%) overnight. Finally, the emulsion was

centrifuged for 30 min at 2500 rpm to obtain supernatant, and the pellets were washed for further characterization.

Determination of entrapment efficiency and drug loading

A 1.5 mL formulation was separated using a Thermo Scientific Heraeus Fresco 17 Centrifuge (Waltham, MA) for 20 min at a speed of 5000 rpm. A 1.0 mL supernatant and 1.0 mL of NaOH 0.1 N were mixed homogeneously, followed by an appropriate dilution with phosphate buffer pH 6.8. The solution was analyzed spectrophotometrically at 234 nm using a Thermo Scientific Genesys 150 UV-Vis Spectrophotometer (Waltham, MA). The concentration of the free drug was calculated according to the response. In addition, the gap between free and total drugs in the system was denoted as encapsulated drug. The encapsulation efficiency (EE) was determined based on the percentage of encapsulated drugs and the total number of drugs in the system. Moreover, the drug loading was also calculated according to the EE (Equation 1).

$$DL = \frac{\text{Entrapped drug (mg)}}{\text{(total weight of polymer (g) + entrapped drug (g))}} \quad (1)$$

Characterization of particle size behaviour

A sample of 50 mL of each formulation was centrifuged at 2500 rpm for 30 min. The solution was homogenized with a vortex until the microparticles were dispersed and transferred into a 10 mL vial. The particle size of the formulation was measured using a laser diffraction particle size analyzer Beckman Coulter LS 13 320 (California, CA). Samples were analyzed in triplicate using a range of 0.017- 2000 µm at a pump speed of 51% and water as the medium. The average particle size was expressed as the volume mean diameter in micrometres.

Determination of particle size distribution

The cumulative particle size profile was constructed according to particle size and cumulative distribution. Particle size below 10%, 50%, and 90% was denoted as d_{10}, d_{50}, and d_{90}, respectively. The distribution of particles was detected with span value and determined according to d_{10}, d_{50}, and d_{90} in Equation 2 (Vo et al., 2020).

$$\text{Span} = \frac{d90 - d10}{d50} \ldots. (2)$$

***In vitro* release of metformin HCl**

The drug release evaluation was performed by weighing the microparticle equivalent to 93,7 mg metformin HCl, then transferred into a dialysis bag (MWCO 12-14 kDa). The test was carried out using an Infors HT Ecotron incubator shaker (Edificio, United Kingdom) with 100 mL phosphate buffer pH 6.8 as medium under a rotational speed and temperature of 100 rpm and 37±0.5°C, respectively. A 2 mL sample was withdrawn at 0, 0.08, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, and 24 h, then replaced by an equal medium volume. Metformin HCl concentration was measured using a Thermo Scientific Genesys 150 Spectrophotometer UV-Vis (Waltham, MA) along with validated analytical method (R^2 of 0.9971, adjusted R^2 of 0.9979, predicted R^2 of 0.996, and accuracy of 107.42%). The drug release profile of each point was analyzed using ANOVA, along with a confidence level of 95% (p=0.05).

***In vivo* antidiabetic activity study**

The in *vivo* transport study used white male Wistar rats as animal models. This method was reviewed and approved by the Research Ethics Committee, Faculty of Medicine, Universitas Muhammadiyah Surakarta, along with an ethical clearance No. 4971/A.2/KEPK-FK UMS/VIII/2023. A total of 9 rats were adopted for seven days and then divided into three groups. On the eighth day, all rats were treated with alloxan at 150 mg/kg BW to induce diabetes mellitus (Daniel et al., 2022). Glucose levels were checked using a principle-based blood glucose indicator on the glucose oxidase biosensor. Glucose level re-evaluation was carried out after three days. If the rats indicated diabetes mellitus by T-test statistical analysis (confidence level of 95%, p=0.05), the treatment was started, along with positive and negative control. The positive control group was given 9 mg/200 g BW conventional suspension orally, the negative control was given alloxan, and the treatment group was given 18 mg/200 g BW prolonged action microparticle. The glucose level was checked at 0, 0.08, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, and 24 h. Blood glucose fluctuation obtained from the highest glucose level to the endpoint of the treatment was analyzed by ANOVA (confidence level of 90%, p=0.1).

Statistical analysis

Each factor was analyzed using a multiple linear regression to calculate the main effect and

interaction. The model was fitted to the given Equation 3.

$$Y = = \beta + a\times A + b\times B + c\times C + ab\times AB + ac\times AC + bc\times BC\ a\times A^2+b\times B^2+c\times C^2 \quad (3)$$

Whereas β is an intercept; a, b, and c are the coefficient regression of the main effect model; and AB, AC, and BC are the coefficient regression of two-factor interaction models. Meanwhile, A, B, and C are factor levels, i.e., percentage metformin HCl in the system, drug loading metformin, and drug-polymer ratio. The model was validated using ANOVA with a confidence level of 95% (p=0.05). The best model had the highest R^2, adjusted R^2, and predicted R^2 and lowest predicted residual error sum of squares. The model should be significant with $p<0.05$, insignificant lack of fit test, and the gap between adjusted and predicted R2 less than 0.2 (Ainurofiq & Choiri, 2018).

RESULTS AND DISCUSSION

Effect on particle size

Particle size significantly affects the release rate of active pharmaceutical compounds (Djukaj et al., 2022). Calculated using multiple linear regression analysis, the particle size was in the range of 0.691 to 2.199 µm. The equation indicated that drug concentration was the most dominant variable, with a 5% contribution in increasing particle size (Table I). Meanwhile, the drug-polymer ratio and Kollidon SR concentration had a negative effect on particle size, with 4% and 0.13% contributions, respectively. Hence, Kollidon SR had an insignificant effect on the particle size. The relationship between drug-polymer ratio and drug concentration was the most influential factor in raising particle size, with a 3-fold higher contribution compared to other interactions. On the other hand, the relationship between the drug-polymer ratio and Kollidon SR concentration, along with that between drug and polymer concentrations, decreased the particle size by 4.31% and 3.92%, respectively.

Parabolic curve response as particle size increased with increasing drug concentration and drug-polymer ratio as the significant factors ($p < 0.05$) (Figure 1a-c), but particle size decreased with excessive drug concentration and drug-polymer ratio. Alipour et al. (2010) stated that a higher concentration of dispersed components resulted in larger particle sizes due to a higher possibility of aggregation (Figures 1a and 1b). However, combining mid-level metformin HCl concentration and drug-polymer ratio produced a greater particle size. A change in Kollidon SR concentration had no significant effect on particle size (Figure 1c). This result was validated in the predicted and actual data plot (Figure S1a; supplementary materials), indicating that all data was spread evenly on the prediction line. Thus, it can be reliably applied to predict the response (Steyerberg et al., 2010).

Effect on drug loading

Drug loading (DL) is a primary requirement for drug delivery, describing the amount of drug entrapped in the microparticle system (Elkateb et al., 2023). The DL was in the range of 11.99 to 492.46 mg/g. Data calculation using multiple linear regression analysis produced an equation quantifying impacting factors (Table I). Metformin HCl concentration was the most dominant variable with a 12.97% positive contribution, followed by drug-polymer ratio with an 11.93% contribution. Concurrently, Kollidon SR concentration had a negative effect on DL by 6.21%, not representing a dominant effect on DL. The relationship between drug-polymer ratio and metformin HCl concentration was the most influential factor in enhancing DL, with a 3-fold higher contribution compared to the other interaction. In contrast, the relationship between drug-polymer ratio and Kollidon SR concentration, along with that between drug and polymer concentrations, decreases the DL by 11.11% and 6.77%, respectively. Ainurofiq et al. (2022) reported that the DL value can be enhanced by increasing the drug load in the systems.

The relationship between the drug-polymer ratio and metformin concentration results in a sloping response contour plot (Figures 1d-f). An increase in drug-polymer ratio and a decrease in metformin concentration increased the DL value (Figure 1d). In contrast, decreasing the drug-polymer ratio and the metformin concentration decreased the DL value (Figure 1e). The DL value also decreased by increasing the drug-polymer ratio and drug concentration (Figure 1f). Additional coalescence of the particles resulted in an integrated matrix, thus lowering drug loading (Zoubari et al., 2019).

Table I. Statistical parameter of critical quality attributes of microparticles

Parameter	Y_1 (mg/g)		Y_2 (µm)		Y_3 (%)		Y_4	
	CR	***Cont***	**CR**	***Cont***	**CR**	***Cont***	**CR**	***Cont***
Intercept	221.87	-	2.07	-	29.13	-	1.07	
A	67.29	11.93	0.0867	4.04	1.92	2.80	0.0470	4.54
B	73.18	12.97	-0.1075	5.01	10.36	15.09	-0.0466	4.50
C	-35.05	6.21	-0.0028	0.13	-4.23	6.16	-0.0164	1.58
AB	134.48	23.84	0.2940	13.71	14.44	21.04	0.0390	3.77
AC	-62.66	11.11	-0.0925	4.31	-5.13	7.47	0.2200	21.25
BC	-38.19	6.77	0.0840	3.92	-7.12	10.37	-0.1372	13.25
A^2	-26.22	4.65	-0.4536	21.16	-8.59	12.51	0.0122	1.18
B^2	30.81	5.46	-0.3951	18.43	4.02	5.86	-0.0530	5.12
C^2	-96.25	17.06	-0.6276	29.28	-12.83	18.69	0.4640	44.81
p	0.0006		0.0085		0.0069		0.1716	
R^2	0.9836		0.9516		0.9557		0.8133	
Adjusted R^2	0.9540		0.8644		0.8760		0.4772	
Predicted R^2	0.7454		0.3394		0.3018		-1.9504	
AP	22.2		9.3648		11.6365		4.8246	

A: Drug-polymer ratio (%); B: Metformin HCl (%); C: Kollidon SR (%); CR: Coefficient of regression; Cont: Contribution (%); Y_1: Drug loading (mg/g); Y_2: Particle size (µm); Y_3: Encapsulation efficiency (%); Y_4: Particle size distribution. R^2: Determination coefficient; Adj. R^2: Adjusted R^2; Pred R^2: Predicted R2; AP: adequate precision

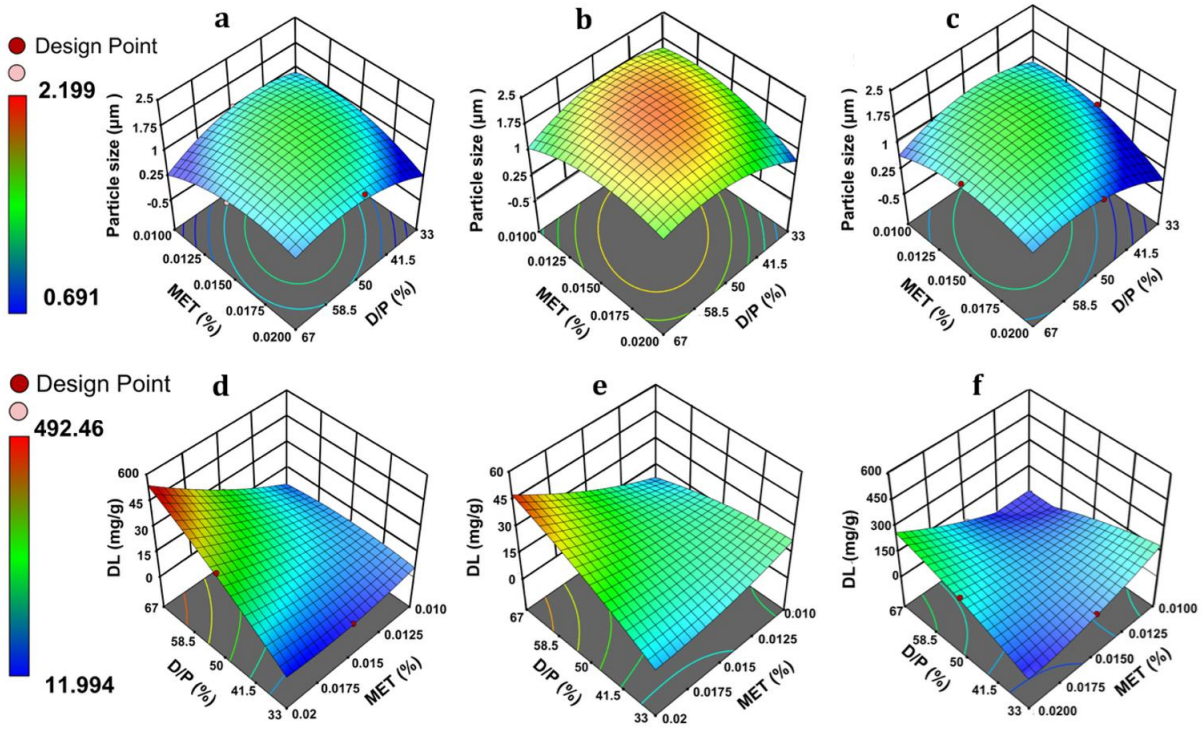

Figure 1. Contour plots of particle size at maximum (a), middle (b), and minimum (c) levels of Kollidon SR and contour plots of drug loading at the maximum (d), middle (e), and minimum (f) levels of Kollidon SR

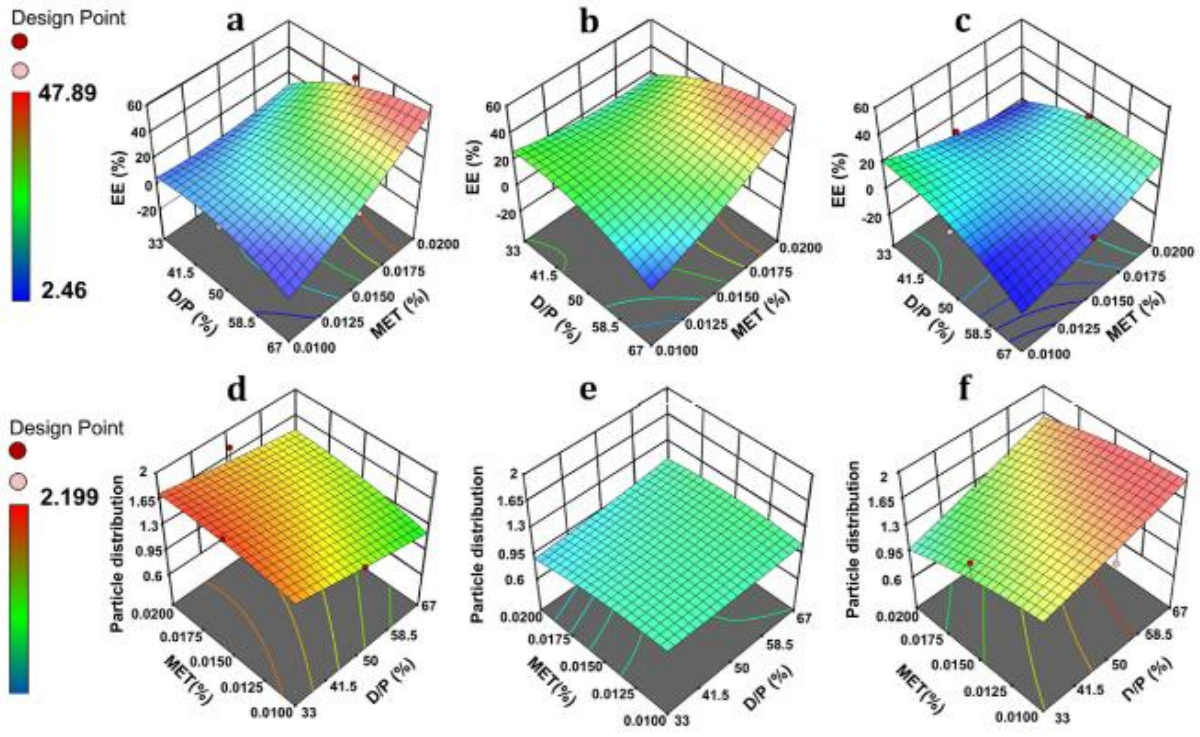

Figure 2. The contour plots of entrapment efficiency (EE) at the maximum (a), middle (b), minimum (c) levels of Kollidon SR and contour plots of the distribution particle at the maximum (d), middle (e), and minimum (f) levels of Kollidon SR

This result was confirmed by the plot of predicted and actual data (Figure S1b; supplementary materials), which shows that all data were scattered on the prediction line and there was no misleading data prediction (Steyerberg et al., 2010).

Effect on entrapment efficiency

Entrapment efficiency (EE) determines the amount of metformin HCl entrapped in the system (Giridhar & Thakur, 2019). High EE is advantageous, indicating that a low carrier level is sufficient to deliver a high dose of the drug (Dhakar, 2012). From data calculated using multiple linear regression analysis, the EE ranged from 2.46 to 47.89%. The equation (Table I) indicated that metformin concentration was the most significant variable, with a 15.09% contribution to increasing EE. Dora et al. (2010) reported similar results indicating increased EE in Eudragit L100 nanoparticles with increasing drug concentration. The drug-polymer ratio also increased EE by 2.80%. On the other hand, Kollidon SR concentration had a negative effect on EE with a 6.16% contribution. The relationship between drug-polymer ratio and metformin concentration was the most influential factor in raising EE, with a 2 to 3-fold higher contribution compared to other interactions. The relationship between the drug-polymer ratio and Kollidon SR concentration, along with that between metformin and Kollidon SR concentrations, decreased the particle size by 7.47 and 10.37%, respectively. This phenomenon was also reported by Sarwar and Hossain (2012), with the lowest potassium losartan content observed in tablets containing the highest concentration of Kollidon SR as a drug release retardant. In addition, Bouriche et al. (2019) found that a higher level of metformin HCl resulted in lower EE. Nonetheless, all variables contribute significantly ($p < 0.05$).

The EE increased with increasing metformin concentration and drug-polymer ratio as the significant factors ($p < 0.05$) (Figures 2a-c). The low drug-to-polymer ratio and decreased metformin concentration resulted in a reduced EE (Figure 2a), while a higher drug-to-polymer ratio also led to a decrease in EE (Figure 2b). According to De et al. (2019), EE increased due to interactions with the methyl functional group of the polymer and the

-NH group in metformin HCl. The Kollidon SR concentration had an insignificant effect, confirmed by the similar patterns of the mid, min, and max curves (Figure 2c). The result was validated by a plot of predicted and actual data (Figure S1c; supplementary materials), in which no misleading data was fitted.

Effect on particle size distribution

Particle size distribution can be assessed as a span value, or the standard deviation around the mean, to determine the relative distribution of particle sizes between 10 and 90% diameter relative to a normalized mid value (Haramkar et al., 2021). The particle size distribution was in the range of 0.691 to 2.199. Analysis by multiple linear regression (Table I) confirmed that no factors significantly affected the particle size distribution. It was proved by no noticeable changes in the contour plots (Figures 2d-f). Preparing microparticle using ultra-homogenizer, particle size distribution has been reported to be mainly affected by mechanical processes rather than the materials used (Vo et al., 2020).

Determination and characterization of optimized formulation

The optimized microparticle formulation was determined based on optimal particle size, drug loading, and entrapment efficiency. The optimized region was obtained from the overlay plot of the three parameters. The optimized microparticle formulation produced a particle size in the range 0.9−1.4 μm, a drug loading of <500 mg/g, and entrapment efficiency of <50%. The optimized formulation was assigned the highest desirability, meeting the target product quality profile to a degree of 91.9%. The optimized region of the microparticle formulation combines metformin HCl 38.2%, Eudragit RS 12.6%, and Kollidon SR 6.2% (Figure 3a). Analysis by optical microscopy confirmed that the microparticles were formed in micro size (Figure 3b). The microparticle size distribution (Figure 3c) indicating an average particle size of 1.363 ± 0.03 μm and a particle size distribution of 1.131 ± 0.028.

Metformin HCl release kinetics

Complete dissolution of metformin HCl from a commercial tablet was achieved in 8 hours, while the complete dissolution of the drug from a prolonged release matrix was not reached until 24 h of testing (Figure 3d). The percentage of drug released at 5, 15, and 30 min (Q_{5min}, Q_{15min}, and Q_{30min}) was 27.98 ± 4.82, 62.24 ± 1.15, and 66.77 ± 0.74 for immediate release tablet dispersion, and 5.85 ± 0.83, 11.63 ± 0.51, and 12.77 ± 0.33 for the prolonged release microparticle formulation, respectively. Significant drug release ($p < 0.05$) was observed as a result of rapid drug dissolution from the particle surface due to the absence of a coating material (Yoo & Won, 2020).

A drug release of 71.13 ± 1.08% followed by plateau release phase has been reported with a conventional tablet dispersion ($p>0.05$). This controlled release was obtained due to dialysis membrane resistance slowing the drug diffusion into the medium (Wolska & Szymańska, 2023). Meanwhile, slow release kinetics from the microparticle formulation were achieved, with 14.12 ± 0.37% drug dissolution after 45 min, demonstrating a significantly lower amount of drug dissolved than by tablet dispersion ($p<0.05$). Wolska & Szymańska (2023) reported similar results in which a cyclosporine dispersion showed a significantly higher dissolution rate than drug-loaded solid-lipid nanoparticles.

Drug release modelling (Table II) represents the release kinetics of the active ingredient with R^2, AIC, and model selection criteria (MSC) as goodness-of-fit parameters (Zuo et al., 2014). The best model was determined by the highest R^2 and MSC, followed by the lowest AIC. Therefore, Weibull was superior in describing metformin HCl release for both microparticles and conventional tablets, with $\beta < 0.75$, indicating that the release of metformin HCl from both formulations followed the Fick diffusion mechanism (Ekenna & Abali, 2022). Thus, metformin HCl release kinetics from the Eudragit RS and Kollidon SR matrix was controlled by drug diffusion through a swellable matrix.

***In-vivo* antidiabetic activity study**

Diabetes mellitus can be induced in rats with alloxan treatment (Figure 3e), evidenced by a significant increase in blood glucose level compared to baseline (p value < 0.01). As reported by Daniel et al. (2022), diabetes mellitus is induced by alloxan through destruction of pancreatic beta cells in the presence of reactive oxygen species. The reduction of blood glucose levels in the negative control group was insignificant compared to the baseline glucose level. Following treatment with the conventional tablets and the microparticle formulation, blood glucose levels after 4 hours decreased by 61.64% and 61.44%, respectively (Figure 3f).

Table II. Statistical parameters of drug release kinetic model of conventional and microparticles formulations

Model	Conventional Tablet				EudRS/KSR Microparticle			
	R^2	AIC	MSC	β	R^2	AIC	MSC	β
Zero Order	0.503	114.454	-1.481	-	0.474	78.852	-.1550	-
First Order	0.790	88.016	0.923	-	0.853	78.286	-1.498	-
Higuchi	0.655	105.504	-0.667	-	0.633	70.064	-0.751	-
Hixson-Crowell	0.624	108.228	-0.915	-	0.479	78.481	-1.516	-
Korsmeyer-Peppas	0.914	73.784	2.216	-	0.909	38.206	2.145	-
Weibull	0.985	55.212	3.905	0.199	0.986	18.300	3.955	0.094

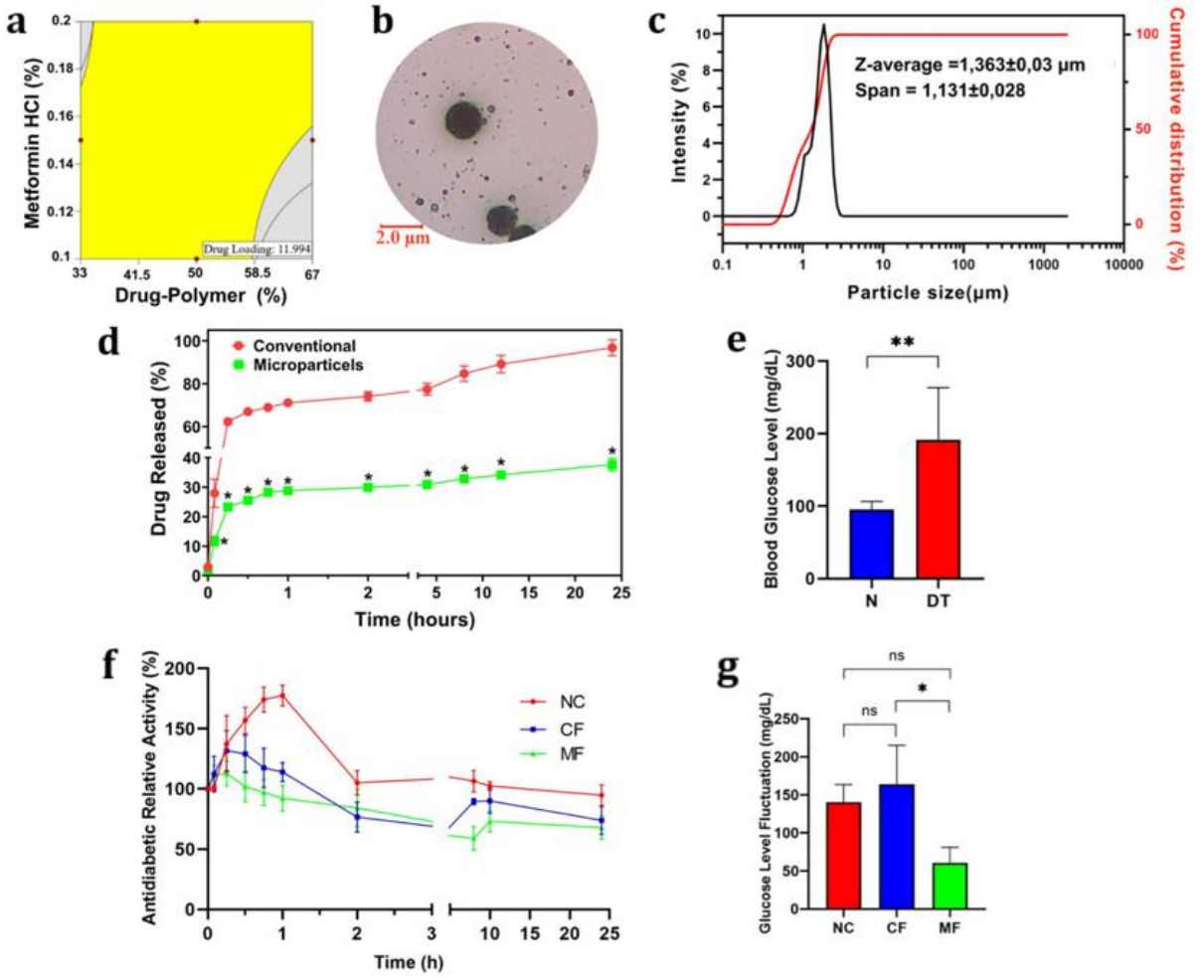

Figure 3. Superimposed contour plot of all responses (a), microscopic photograph of the optimized microparticle (b), particle size distribution of the optimized formulation (c), drug release profiles (d), blood glucose level after alloxan induction (e), antidiabetic relative activity after treatment (f), blood glucose fluctuation (g). N, normal group; DT, diabetes treatment; NC, negative control; CF, conventional formulation; MF, microparticle formulation. Data was presented as mean±SD, n=6, ns = $p>0.05$, * = $p<0.05$, ** = $p<0.01$.

However, the decrease in the conventional tablet group was not lasting, with blood glucose levels rising to 89.48% after 8 hours. The microparticles reduced blood glucose levels by 59.02% after 24 hours compared to the conventional tablet. Further analysis (Figure 3g) revealed that the microparticles conferred the lowest blood glucose level fluctuation compared to the other two groups and resulted in significantly lower fluctuation compared to the conventional tablet group ($p < 0.05$).

This work demonstrates the successful DoE-optimized formulation of sustained release microparticles of Kollidon SR and Eudragit RS as a matrix combination containing metformin HCl. These microparticles could control blood glucose levels by sustained release. However, the formulation requires development into suitable solid dosage forms before administration. By incorporating sustained release microparticles, the dosage form will be breakable and chewable, unique features differentiating them from other sustained-release dosage forms. In addition, an orally disintegrating formulation would be a promising candidate for further delivery strategies.

CONCLUSION

A microparticle formulation based on Eudragit RS and Kollidon SR for sustained release of metformin HCl was successfully developed using Box-Behnken experimental design. Metformin HCl concentration and drug-polymer ratio were dominant factors increasing particle size, drug loading, entrapment efficiency, and particle size distribution. Particle size analysis revealed that the optimized formulation was micro-sized and presented a narrow size distribution. The microparticle formulation effectively controlled drug release and effected sustained reduced blood glucose levels in a rat model of diabetes mellitus.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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