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Formulation and Optimization of Imeglimin-Loaded Nanoparticles Using Central Composite Design

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KEYWORDS

Imeglimin, Polymeric Nanoparticles, Chitosan, Sodium Alginate, Controlled Release, CCRD, Type 2 Diabetes Mellitus

ABSTRACT:

Type 2 diabetes mellitus (T2DM) is increasing as a worldwide health issue. Imeglimin, a first-in-class oral antidiabetic compound, exerts potential therapeutic activities via several mechanisms, including enhanced mitochondrial function and glucose-stimulated insulin secretion. Despite this, it is still a challenge to increase its oral bioavailability. The purpose of this work was to prepare and optimize Imeglimin-loaded polymeric nanoparticles (IG-PNs) based on chitosan and sodium alginate to enhance entrapment and extended release of the drug for oral delivery. IG-PNs were synthesized through ionotropic gelation and were optimized through a Central Composite Rotatable Design (CCRD). The influence of chitosan and sodium alginate concentration, and stirring speed, was tested on particle size (PS) and entrapment efficiency (EE). The characterization involved dynamic light scattering, zeta potential, scanning electron microscopy, and in vitro release studies. The optimized formulation had a particle size of 126.75 ± 2.39 nm, PDI of 0.228 ± 0.040, and EE of 85.50 ± 5.87%. The zeta potential was −12.8 ± 2.42 mV, and SEM micrographs revealed spherical, uniform particles. Release studies in vitro revealed 80.79 ± 7.33% cumulative release in PBS (pH 7.4) and 14.62 ± 1.87% in 0.1 N HCl, and release kinetics were best described by Korsmeyer-Peppas and zero-order models, respectively. The optimized IG-PNs indicated improved drug entrapment and controlled release, indicating better oral delivery promise for Imeglimin. These results justify more preclinical and clinical investigation.

1. Introduction

Type 2 diabetes mellitus, or T2DM, is an urgent and critical health issue on a global level, currently affecting the lives of over 380 million people worldwide. Furthermore, estimates suggest that this figure may rise to exceed 590 million people by the year 2035 if trends persist. The increasing prevalence of T2DM is directly linked to a range of factors, including an increasingly aging population, rapidly increasing rates of obesity, as well as specific ethnic groups that are deemed to be at high risk. Imeglimin is the first drug in a new class of oral antidiabetic drugs that are all members of a broad class referred to as 'glimins.'[6]The journey to its discovery was founded on in vivo phenotypic screening performed to evaluate its antihyperglycemic activity using rodent models, followed by strategic chemical optimization performed to optimize a lead molecule.[1][2][3] Recent and landmark phase III clinical trials performed in Japan have shown that Imeglimin has strong and long-lasting antihyperglycemic effects, as well as a safety profile and level of tolerability that are considered to be favorable. Notably, this drug does not cause severe hypoglycemia, thus making it a valuable and promising therapeutic agent for the treatment of T2DM in affected individuals. Imeglimin operates through a multifaceted mechanism to

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enhance glycaemic control in individuals with type 2 diabetes (T2DM). Here are the key components of its action:

- Amplification of Glucose-Stimulated Insulin Secretion (GSIS): Imeglimin enhances insulin secretion in response to glucose by increasing the ATP/ADP ratio within pancreatic β-cells. This elevation in intracellular energy status plays a vital role in facilitating effective glucose-stimulated insulin release.[5]
- Preservation of Beta Cell Mass: The drug helps maintain the mass of beta cells, preventing their apoptosis (cell death) and promoting their survival, which is vital for sustained insulin production.[7][8]
- Enhanced Insulin Action: Imeglimin improves insulin sensitivity in both the liver and skeletal muscles. This leads to better glucose uptake and utilization, which is essential for managing blood sugar levels.
- Inhibition of Hepatic Glucose Output: It reduces glucose production in the liver, contributing to lower blood sugar levels, which is a critical aspect of diabetes management.[9][10][11]
- Improvement of the Mitochondrial Function: Imeglimin enhances mitochondrial function by increasing the ATP/ADP ratio, which is important for the energy production and overall cellular health. This improvement supports better insulin action and metabolic function.
- Reduction of Oxidative Stress: The drug reduces oxidative stress, which can improve insulin sensitivity and overall metabolic function, further aiding in the management of T2DM.

Imeglimin Hydrochloride is a potent drug against diabetes as it specifically targets mitochondrial bioenergetics. Also, Imeglimin hydrochloride has low chances of hypoglycaemia. Even though there are other anti-diabetic drugs available, Imeglimin hydrochloride appears to be good option for diabetes patients. It is safer, more potent, and better tolerated compared to alternatives.[4][12]

2. Material

Imeglimin hydrochloride was procured from CTX Life science, Gujrat. Natural Polymer Sodium alginate was procured from. Chitosan was procured from SM Pharma and Chemicals, Mumbai. Marketed Imeglimin hydrochloride tablets the materials were obtained from a local dispensary in Pune. All other chemicals used were of analytical grade.

3. Method of Preparation

The nanoparticles developed using the ionic gelation technique, assisted by magnetic stirring. Alginate/chitosan nanoparticles were prepared through a two-step process involving the initial ionotropic pre-gelation of the polyanion (alginate) with calcium chloride, followed by subsequent interaction with chitosan polycationic crosslinking. Calcium chloride solution was added drop wise for 30 min under gentle stirring (800 rpm) into a beaker containing Sodium alginate solution and imeglimin hydrochloride to provide an alginate pre-gel. Then different concentration of chitosan solution was added drop wise into the pre-gel the nanoparticles were stirred for 30 minutes to enhance curing, followed by centrifugation at 15,000 rpm for approximately 35 minutes at 4 °C to collect the final product.[13][14][15]

4. Experimental Design

- Optimization of Imeglimin loaded Polymeric Nanoparticles

Optimization of the nanoparticle formulation was performed using Design Expert software (version 12, Stat-Ease Inc., Minneapolis, USA). A CCRD, a widely used experimental design approach, employed to optimize the formulation parameters. The objective was to achieve a formulation with an optimal PS, low PDI, and high EE.

Three independent variables were selected for the experimental design: sodium alginate concentration (2–3% w/v), chitosan concentration (3–5% v/v), and stirring speed (600–800 rpm). Using these parameters, the Central Composite Rotatable Design (CCRD) generated a total of 20 experimental runs. As outlined in Table 4, the selected variables were evaluated for their influence on two dependent responses—particle size and entrapment efficiency. The ranges for the independent variables were determined based on preliminary screening and trial-and-error studies.[16][17]

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5. Characterization Of Nanoparticles

ENTRAPMENT EFFICIENCY (EE)

Prepared Imeglimin-loaded polymeric nanoparticles was centrifuged at 15,000 rpm for 90 minutes at 4 °C using a refrigerated centrifuge (Eppendorf 5415 R, Germany). The resulting supernatant was collected to determine the amount of unencapsulated Imeglimin. Then sample was diluted with methanol and filter via 0.25 µm membrane filter. The filtrate was then analyzed for Imeglimin content using a UV spectrophotometer at 240 nm. The amount of drug encapsulated within the nanoparticles was calculated using the following equation:

$$EE\% = \frac{(Wx - Wy)}{(Wx)} \times 100$$

Here, W_x represents the total amount of Imeglimin used, while W_y corresponds to the amount of Imeglimin present in the supernatant.[20][27]

PARTICLE SIZE AND POLY DISPERSIBILITY INDEX

Particle size and associated parameters were measured using a Horiba SZ-100V2 instrument. DLS was employed to determine PS. Prior to analysis, samples were diluted tenfold with Milli-Q water to achieve uniform dispersion and were analyzed at a scattering angle of 90° and 25 ± 2 °C temperature.[21][23][24]

ZETA POTENTIAL

Zeta potential was measured using the Horiba SZ-100 series instrument, which calculates this parameter based on the electrophoretic mobility of nanoparticles in an applied electric field. For the analysis, the nanoparticle suspension was appropriately diluted with Milli-Q water and introduced into the sample chamber for measurement.[20][25]

SURFACE MORPHOLOGY

IG-PNs formulation were examined the surface morphology of the nanoparticle formulation at pH 7.4 was examined using a JEOL JSM-840A SEM. The samples were mounted on an aluminium mount and then were critical point dried and imaged using a scanning electron microscope.[28]

IN-VITRO DRUG RELEASE PARAMETER

Analytical procedures were conducted using dialysis pouch with molecular weight of 10–12 kDa (HiMedia, India). Total of 4 mL of Imeglimin-loaded polymeric nanoparticles (IG-PNs), equivalent to 50 mg of Imeglimin, were placed into a dialysis membrane and immersed in 900 mL of two different dissolution media: The study was performed with the help of USP Type II dissolution apparatus, operated at a stirring speed of about 50 rpm and 37 ± 0.5 °C, in both 0.1 N HCl and PBS, pH 7.4.

At specified time intervals (0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours), 1 mL samples was withdrawn and replaced with equal volume of dissolution medium for maintaining sink conditions. Collected samples were diluted and analysed for Imeglimin content using a UV spectrophotometer at 240 nm. The cumulative percentage of drug release was calculated using the equation provided below. The drug release data were then fitted into various kinetic models—namely first order, zero-order, Korsmeyer–Peppas, and Higuchi to evaluate the release kinetics and underlying drug release mechanism.[20][23][26]

$$\%\ Drug\ release = \frac{Conc.(\mu g/ml) \times DF \times Vol.of\ release\ medium(ml)}{Initial\ dose\ (\mu g)} \times 100$$

Here, DF = Denotes Dilution Factor

Results

- **FORMULATION COMPOSITION OPTIMIZATION**

A total of 20 experimental runs were generated by incorporating the selected independent and dependent variables into the Central Composite Rotatable Design (CCRD). Based on these runs, multiple nanoparticle formulations were developed. Each formulation was then evaluated for EE and PS.[17][18][19] The variables and corresponding data are summarized in Table 1.

Table 1. The Formulations were Evaluated for Their Entrapment Efficiency and Particle Size

	Factor 1	Factor 2	Factor 3	Response 1	Response 2
Run	A: Chitosan	B: Sodium Alginate	C: Stirring speed	Particle Size	Entrapment Efficiency
	%w/w	%w/w	rpm	nm	%

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1	0.15	0.251134	700	278	49
2	0.1	0.2	800	268	49
3	0.15	0.125	700	130	81
4	0.15	0.125	700	129	83
5	0.1	0.05	800	143	75
6	0.2	0.05	600	198	80
7	0.1	0.05	600	162	47
8	0.2	0.2	600	225	58
9	0.1	0.2	600	265	74
10	0.0659104	0.125	700	200	87
11	0.15	0.125	868.179	240	56
12	0.15	0.125	700	125	92
13	0.23409	0.125	700	235	76
14	0.15	0.125	531.821	154	50
15	0.15	0.125	700	127	93
16	0.2	0.05	800	176	68
17	0.15	0.125	700	126.5	79
18	0.2	0.2	800	215	51
19	0.15	0.125	700	126	88
20	0.15	-0.00113446	700	192	55

- **RESPONSE SURFACE EXPLORATION**

EFFECT OF INDEPENDENT FACTORS

1) PARTICLE SIZE

The PS of Imeglimin-loaded polymeric nanoparticles (IG-PNs) were found to range between 125 and 278 nm. The derived quadratic model indicated a statistically significant influence of polymer concentration and stirring speed on particle size ($p < 0.0005$). An increase in polymer concentration was associated with a corresponding increase in particle size, likely due to the enhanced viscosity and solid content in the formulation. Conversely, higher stirring speeds contributed to a reduction in particle size, likely due to increased shear forces that promote particle breakdown during formation. The combined effects of variables on particle size are shown in Figure 2. Both the amount of Chitosan and Sodium alginate in combination shows negative impact. Similarly, sodium alginate concentration and stirring speed collectively had a detrimental impact on the PS. However, in contrast, the stirring speed and amount of chitosan had a positive effect on the size of the particles.[21][23][24]

PS (R1) = 127.75 + 2.55*A + 32.12*B + 7.08*C – 20.25*AB – 2.00*AC + 4.25*BC + 28.66*A2 + 34.84*B2 + 21.41*C2.

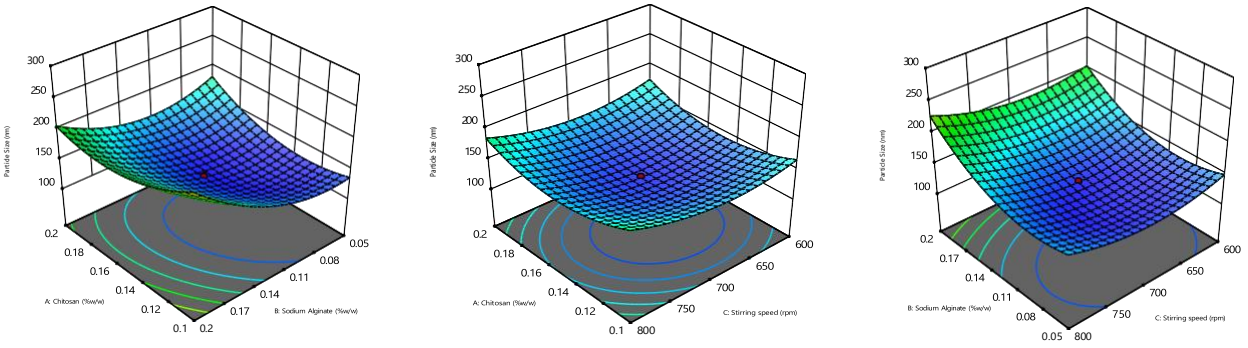

Fig.2. Effects of Variables on PS

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2) ENTRAPMENT EFFICIENCY

The EE values across all experimental runs ranged from 52.22% to 92.54%. The effects of the independent variables on the EE of IG in the polymeric nanoparticles were statistically significant ($p < 0.0001$), resulting in both increases and decreases in EE depending on the factor levels. The derived quadratic polynomial equation indicated that increasing the polymer concentration contributed to enhanced entrapment efficiency. An increase EE was observed, likely because of higher amount of drug being successfully encapsulated within the formulation. This enhancement in EE can also be attributed to the increased polymer concentration, which results in the formation of multiple polymeric layers around the nanoparticles, thereby promoting more effective drug entrapment. Moreover, an increase in stirring speed positively influenced EE by facilitating more efficient dispersion and incorporation of the drug into the nanoparticles. The mechanical shear at higher stirring speeds may help disrupt larger aggregates, creating more surface area and enabling further drug encapsulation. The combined effects of polymer concentration, surfactant presence, and stirring speed on EE are illustrated in Figure 3. Overall, polymer content and stirring speed were found to have a significant and positive impact on Imeglimin entrapment efficiency. A detrimental effect was observed when and Stirring speed were utilized together with polymer concentration and stirring speed.[20][27]

$EE\ (R2) = 85.93 - 0.4759 *A - 3.52*B - 0.4327*C - 5.00*AB - 2.75*AC - 6.00 *BC - 1.16A^2 - 11.59 B^2 - 11.24C^2$.

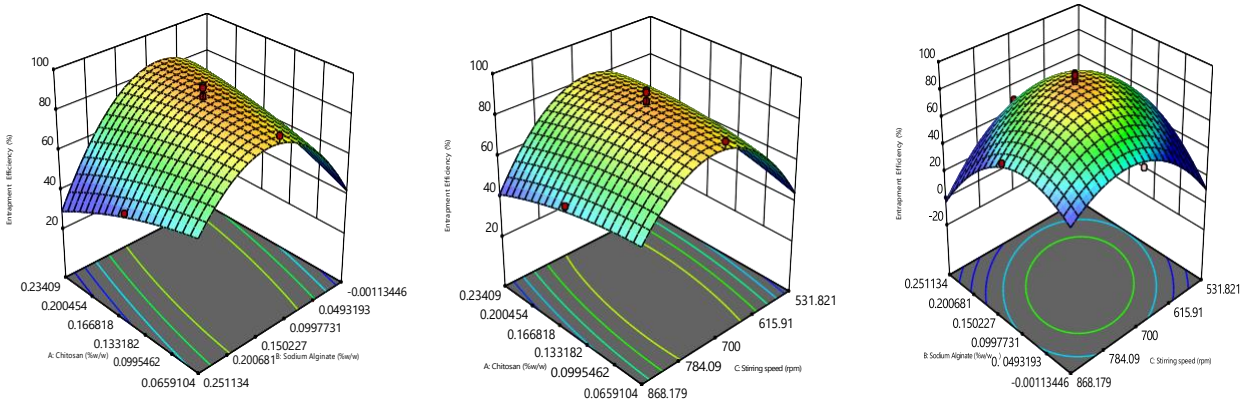

Fig. 3. Effect of Variables on EE

- **DESIGN VALIDATION**

The CCRD was employed to optimize the formulation for achieving the desired particle size (PS) and entrapment efficiency (EE). Optimal values for both independent variables and response parameters were estimated through the model. Based on these optimized conditions, Imeglimin-loaded polymeric nanoparticles (IG-PNs) were prepared accordingly. The experimental outcomes was in close agreement with the predicted values, confirming the accuracy and robustness of the optimization process.[16][17]

- **OPTIMIZED COMPOSITION FOR THE MANUFACTURING OF IG PNS**

Subsequently, using the optimized IG PNs, obtained after CCRD application, with 0.15 % w/v chitosan and 0.125 % w/v of the concentration of sodium alginate, stirring speed 700 rpm. The IG formed was mixed with the chitosan to encapsulate the drug, and finally the addition of it into sodium alginate and calcium chloride. This newly developed product was then characterized by various characteristics features[22].

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Table.2. Dependant and Independent variables used in CCRD.

Independent Factors			Levels Used				
Factor	**Name**	**Units**	**Axial**	**Low (-1)**	**Medium (0)**	**High (+1)**	**Axial**
A	Chitosan	%w/w	0.0659	0.10	0.1500	0.20	0.2341
B	Sodium Alginate	%w/w	-0.0011	0.05	0.1250	0.20	0.2511
C	Stirring speed	rpm	531.82	600.00	700.00	800.00	868.18
Dependent Factors **R1 – Particle size (nm)** **R2 – Entrapment efficiency (%)**				**Constraints** Lower Higher			

6. Result And Discussion

- **CHARACTERIZATION OF OPTIMIZED IG PNS**

i) PARTICLE SIZE AND PDI

The optimized IG PNs formulation developed had a PS of 126.75 ± 2.39 nm and Poly dispersibility Index of 0.228 ± 0.040, as shown in Fig. 4. Particle size (PS) of the Imeglimin polymeric nanoparticles (IG-PNs) was found to be within the optimal range for oral delivery, making it suitable for further formulation development. This appropriate size distribution is expected to facilitate effective release of Imeglimin at the targeted site, potentially contributing to the therapeutic modulation of diabetes mellitus. Additionally, the observed polydispersity index (PDI) values ranged between 0.0 and 1.0, indicating the absence of particle aggregation. This suggests that the formulation exhibits good physical stability and uniform particle distribution.[21][23][24]

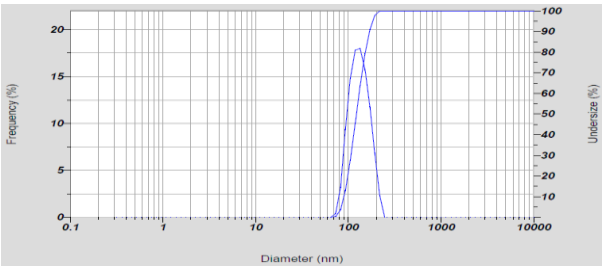

Fig.4. PS and PDI of IG-PNs optimized formulation

ii) EE

The entrapment efficiency (EE) of the Imeglimin-loaded polymeric nanoparticles (IG-PNs) was determined to be 85.50 ± 5.87%, indicating that a substantial proportion of Imeglimin was successfully encapsulated within the polymer matrix used in the formulation.[20][27]

iii) ZETA POTENTIAL

The average ZP of the optimized IG-PN formulation were measured to −12.8 ± 2.42 mV, as depicted in Figure 5. Although this value does not fall within the generally accepted stability threshold of < −25 mV or > +25 mV, it still suggests a moderate level of colloidal stability. The relatively negative surface charge helps prevent particle aggregation to some extent, contributing to the physical stability of the formulation. The absence of significant aggregation further supports the uniformity and dispersion quality of the nanoparticles.[20][25]

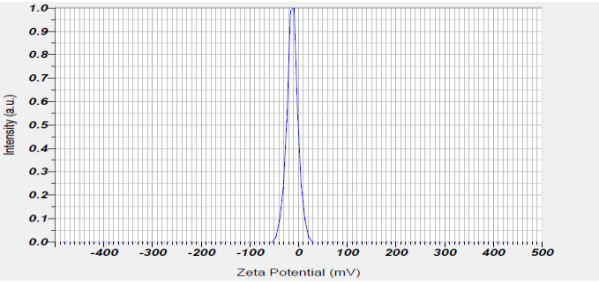

Fig.5. ZP of the optimized IG-PNs

iv) SURFACE MORPHOLOGY

The morphology of IG-PNs were examined by SEM, as indicated in Fig. 6, where it is noticeable that the particles were round shape in prepared formulation with black margins and diameter smaller than 200 nm. The picture serves to illustrate the fact that the loaded IG is well encapsulated within the polymers.[28]

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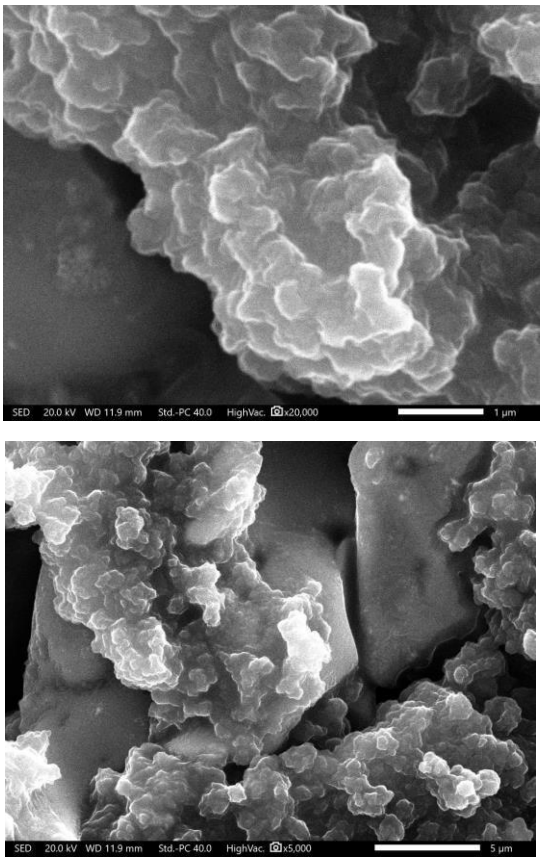


Fig. 6. SEM image of the optimized IG-PNs.

v) IN-VITRO DRUG RELEASE ANALYSIS

The cumulative release of Imeglimin from IG-loaded polymeric nanoparticles (IG-PNs) and conventional IG tablets in 0.1 N HCl was 14.62 ± 1.87% and 11.02 ± 1.99%. PBS, pH 7.4, IG-PNs exhibited a release of 80.79 ± 7.33%, while the tablets showed 75.63 ± 8.46%, as shown in Figure 7. The initial burst release observed with IG-PNs may be attributed to the presence of IG loosely bound or located near the surface of the polymeric matrix. This phenomenon supports the sustained release behaviour of the formulation. The progressive penetration of the aqueous medium into the inner matrix of the nanoparticles facilitates the dissolution of IG, contributing to the continued drug release over time. Moreover, the higher polymer concentration and slightly porous nature of the nanoparticles are likely responsible for the enhanced release efficiency observed in IG-PNs compared to the conventional tablet formulation. Drug release kinetics were analysed using various mathematical models, as presented in Figures 8 and 9. In 0.1 N HCl, the release of drug the nanoparticles best fit a zero-order kinetic model, whereas in phosphate-buffered saline (PBS, pH 7.4), the Korsmeyer–Peppas model showed the highest correlation based on the coefficient of determination (R^2). The n value obtained from the Korsmeyer–Peppas model in PBS was 0.38, indicating a Fickian diffusion mechanism, as it falls below the threshold value of 0.43.[20][23][26]

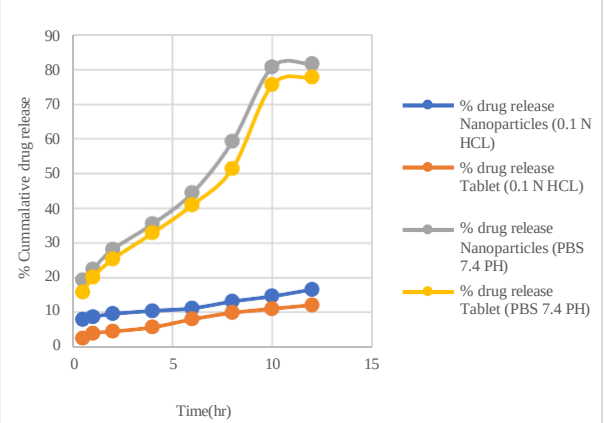
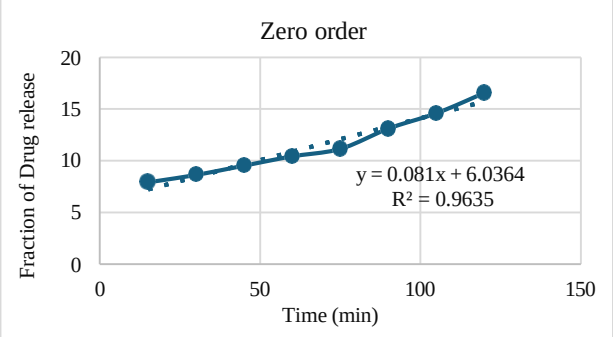
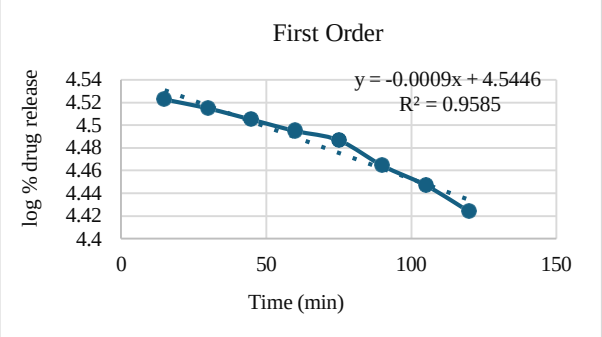


Fig. 7. Release study of IG from IG-PNs and the conventional tablet was conducted in 0.1 N HCl and PBS, pH 7.4





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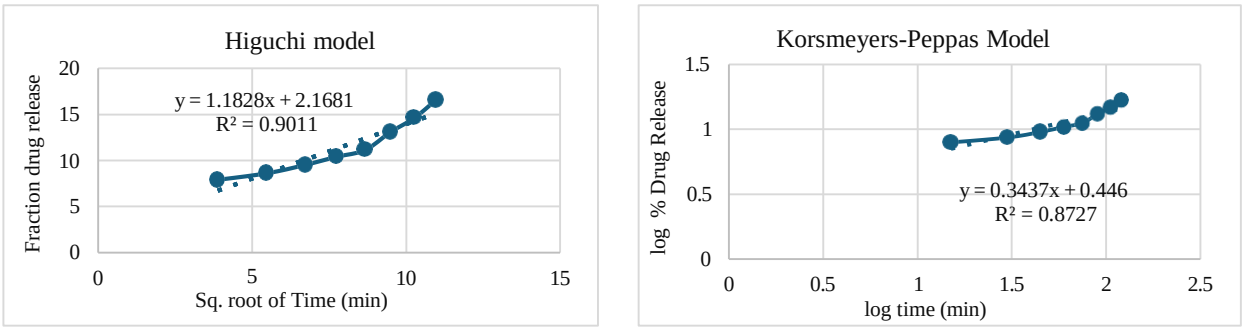

Fig. 8. Release profile of drug from IG-PNs formulation by different kinetic models in 0.1 N HCl

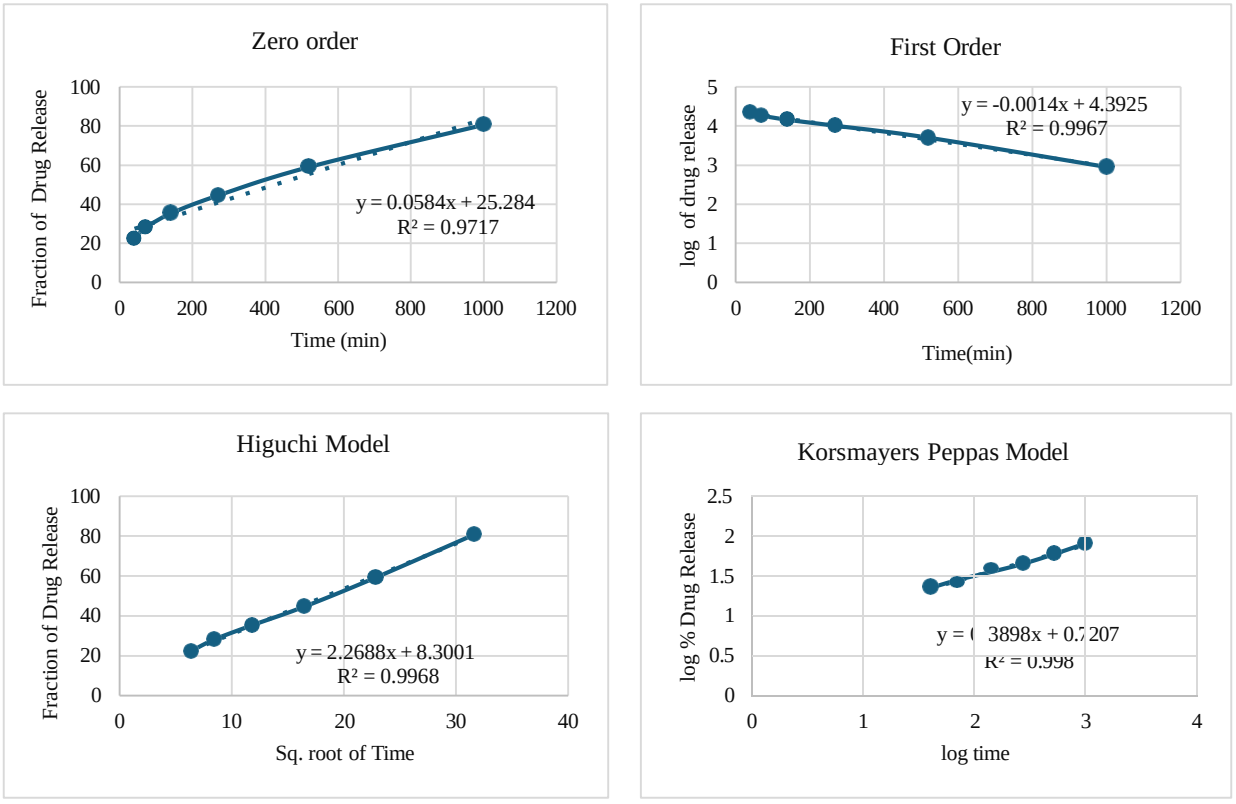

Fig. 9. Release profile of IG from the IG-PNs formulation in PBS (pH 7.4) by using various kinetic models.

DISCUSSION

The particle size (PS) of the synthesized Imeglimin- The particle size of the drug-loaded polymeric nanoparticles (IG-PNs) ranged from 125 to 278 nm. According to the design of experiments (DOE) analysis, the combined concentrations of chitosan and sodium alginate exhibited a negative effect on PS.

Similarly, the interaction between sodium alginate concentration and sonication time also exhibited a detrimental effect on PS. In contrast, as chitosan concentration increases and stirring speed showed a positive influence, contributing to a reduction in PS.

Regarding entrapment efficiency (EE), increasing the overall polymer concentration resulted in higher EE, attributed to greater drug entrapment within the nanoparticle matrix. Specifically, increasing chitosan concentration led to improved EE, likely due to the formation of multiple polymer layers encapsulating the drug within the particles.

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Following optimization via Central Composite Rotatable Design (CCRD), the final IG-PN formulation was developed using 1.5% w/w chitosan, 1.25% w/w sodium alginate, and a stirring speed of 700 rpm.

The drug release studies revealed that the cumulative release of IG from IG-PNs and the conventional IG tablet in 0.1 N HCl was 14.62 ± 1.87% and 11.02 ± 1.99%, respectively. In PBS, pH 7.4, IG-PNs exhibited a release of 80.79 ± 7.33%, compared to 75.63 ± 8.46% from the conventional tablet. These results confirm that the nanoparticle-based formulation of IG enhances drug release and suggests superior therapeutic potential when compared to the conventional tablet form.

7. Conclusion

Using the Central Composite Rotatable Design (CCRD), Imeglimin-loaded polymeric nanoparticles (IG-PNs) were successfully formulated and optimized. The resulting formulation demonstrated the desired physicochemical characteristics suitable for oral delivery to the target site. Compared to the conventional tablet form, the optimized IG-PNs exhibited a more controlled and enhanced release profile of Imeglimin. Furthermore, the formulation showed promising antidiabetic potential, indicating its capability to improve both the therapeutic efficacy and oral bioavailability of Imeglimin.

In conclusion, the study validates successful development and optimization of IG-PNs as a promising oral delivery system for Imeglimin. However, the absence of clinical data remains a limitation. Future clinical investigations are necessary to further establish the therapeutic efficacy, safety profile, and benefit–risk ratio of the formulation in humans.

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