RESEARCH ARTICLE

Formulation and Evaluation of Multiparticulate Pellet Systems for Antidiabetic and Antihypertensive Drugs: Application of Extrusion–Spheronization and Solution Layering Techniques

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ABSTRACT

The present study focuses on the development and comprehensive evaluation of sustained and controlled release multiparticulate pellet formulations for three therapeutic agents: Tolbutamide, Saxagliptin, and Verapamil. The primary objective was to enhance drug release profiles and patient compliance using extrusion–spheronization and solution layering techniques. Tolbutamide and Verapamil were formulated into matrix-based sustained release pellets using hydrophilic polymers (HPMC) and plasticizers (MCC), while Saxagliptin pellets were prepared via solution layering on nonpareil seeds with optional Eudragit RS 100 coating for controlled release. Optimization of formulation parameters was performed using factorial design.All formulations exhibited excellent flow properties, narrow particle size distribution (500–850 µm), and satisfactory morphology with minimal friability (<1%). Drug content uniformity across all batches remained within pharmacopeial limits (RSD < 2%). *In vitro* drug release studies showed that Tolbutamide was released steadily (98.7% in 5 hours), Saxagliptin was released in a zero-order controlled way (98.1% in 5 hours), and Verapamil was released in a pH-sensitive way (92.5% in 6 hours). These results fit Higuchi, zero-order, and first-order kinetic models, respectively. These results show that pelletization methods can be used to customize the release kinetics of drugs with different physical and chemical properties and therapeutic goals. This shows that they are good for making strong oral controlled release dosage forms.

Keywords: Multiparticulate Pellet Systems, Antidiabetic, Antihypertensive,Pelletization

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INTRODUCTION

In current years, sustained release (SR) drug delivery systems have gatheredmajorconsideration due to their capability to sustain consistent plasma drug concentrations, expand therapeutic effectiveness, and improve patient compliance.[1,2] Distinct conservative dosage forms that frequentlyinvolve multiple daily administrations, SR formulations offer controlled release, so reducing dosing occurrence and minimizing variations in drug levels in systemic circulation[3,4]. Amongst several SR technologies, pelletizationby extrusion-spheronization has arisen as a capable system for developing multiparticulate dosage forms by even shape, surface, and reproducible drug release profiles[5].

Saxagliptin, a powerful dipeptidyl peptidase-4 (DPP-4) inhibitor, is extensively used for the diabetes. It improves glycemic control by collective incretin levels, which in chance stimulates insulin excretion and conquers glucagon release[6]. Despite its clinical efficiency, Saxagliptin has a relatively small half-life of almost 2.5 hours, requiringnormal administration to retainbeneficial levels. This pharmacokinetic limitation makes it aperfect candidate for sustained release formulation, expected at improving patient adherence and provided that long-term glycemic control[7].

The extrusion-spheronization method offers some advantages for formulating sustained release pellets. This developmentpermits the assimilation of high drug loads and lets for the use of many polymers and excipients to modify drug release[8]. In this study, hydrophilic polymers such as HPMC K100M and ethyl cellulose were employed as matrix formers and release retardants[9]. Microcrystalline cellulose (MCC) was used as a spheronization aid to improve pellet formation and structural integrity[10].

The current research emphases on the formulation, optimization, and estimation of sustained release pellets of Saxagliptinby the extrusion-spheronization method[11]. The prepared pellets were imperiled to inclusive physicochemical and *in vitro* dissolution studies to evaluate their morphology, mechanical strength, drug content, and release kinetics. This study purposes to improve a robust SR formulation of Saxagliptin that could possiblyexpand therapeutic outcomes and patient superiority of life[12].

MATERIALS AND METHODS

Differential Scanning Calorimetry (DSC)

Compatibility between the selected drugs (Tolbutamide, Saxagliptin, and Verapamil) and various excipients was assessed using DSC (Mettler Toledo). Samples (2–5 mg) of pure drugs, excipients, and their 1:1 physical mixtures were

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Table 1: 3^2 Factorial Design

Batch	X_1 (Polymer %)	X_2 (Binder %)
F1	5	2
F2	5	4
F3	5	6
F4	10	2
F5	10	4
F6	10	6
F7	15	2
F8	15	4
F9	15	6

Table 2: Tolbutamide Pellets composition

Batch	Polymer (%)	Binder (%)	Drug Content (%)
F1	5	2	98.7
F2	5	4	99.5
F3	5	6	97.8
F4	10	2	100.1
F5	10	4	101.3
F6	10	6	99.4
F7	15	2	97.9
F8	15	4	98.6
F9	15	6	99.8

Table 3: Saxagliptin Pellets composition

Batch	Polymer (%)	Binder (%)	Drug Content (%)
F1	5	2	100.4
F2	5	4	98.9
F3	5	6	99.6
F4	10	2	101.1
F5	10	4	100.3
F6	10	6	98.7
F7	15	2	99.2
F8	15	4	98.4
F9	15	6	97.8

hermetically sealed in aluminum pans and heated from 25°C to 300°C at a rate of 10°C/min under a nitrogen purge (40 mL/min). Thermograms were analyzed for characteristic melting points and enthalpy changes (ΔH). Shifts, disappearance, or broadening of peaks in physical mixtures were interpreted as potential incompatibilities.

FTIR Study

FTIR spectroscopy was conducted to further evaluate drug-excipient interactions. Spectra were recorded (4000–400 cm^{-1}, resolution 4 cm^{-1}, 32 scans) using KBr pellet method. Each drug and its physical mixture with excipients (1:1 w/w) were examined for characteristic functional group peaks.

Pellet Formulation Development

Pelletization techniques were selected based on drug properties and intended release profiles. Two methods were employed:

Extrusion–Spheronization for Tolbutamide and Verapamil (low solubility, sustained release)

Solution Layering for Saxagliptin (better solubility, controlled release)

Formulations were optimized using a 3^2 factorial design, assessing:

X_1: Polymer concentration (5%, 10%, 15%)

X_2: Binder concentration (2%, 4%, 6%)

Nine formulations (F1–F9) were prepared for each drug to study the impact of these variables on pellet characteristics and drug release.

Pelletization Methods

A. Extrusion–Spheronization (Tolbutamide& Verapamil)

Drugs were mixed with HPMC, MCC, and PVP K30 binder, then granulated to form a cohesive mass. The wet mass was extruded (1 mm screen) and spheronized (1000 rpm, 3–5 min). Pellets were dried at 40–45°C to a constant weight.

B. Solution Layering (Saxagliptin)

A drug-polymer solution (Saxagliptin + HPMC) was sprayed onto nonpareil seeds (20/25 mesh) using a fluidized bed processor. After reaching the desired drug load, pellets were dried and optionally coated with Eudragit RS 100 for controlled release.

All batches (F1–F9) were stored in airtight containers for further evaluation.

Drug-Specific Formulation Strategies

Tolbutamide: Sustained release matrix pellets via extrusion–spheronization with HPMC, MCC, and PVP K30.

Saxagliptin: Controlled/immediate release via solution layering onto inert cores; optionally coated with Eudragit RS 100.

Verapamil: Sustained release using extrusion–spheronization; optional enteric coating with Eudragit L100/S100.

Formulation Optimization

A 3^2 factorial design evaluated the effects of polymer (5–15%) and binder (2–6%) concentrations on:

Pellet size & sphericity

Drug content & loading

In vitro drug release

Pellet Evaluation Parameters

Flow Properties

Angle of Repose: Indicative of flowability.

Bulk & Tapped Density: Used to calculate Carr's Index and Hausner Ratio.

Carr's Index&Hausner Ratio: <15% and <1.25 indicate good flow.

Particle Size Analysis

Sieve Analysis and *Laser Diffraction* (D10, D50, D90 values) for size distribution.

Morphology (SEM)

Examined surface texture, shape, and porosity.

Friability

Pellets subjected to mechanical abrasion (100 revolutions, 25 rpm). Acceptable if <1% weight loss.

Drug Content Uniformity

Assessed using UV or HPLC. Pellets dissolved, filtered, and analyzed against calibration standards. Acceptable range: 85–115% of label claim.

In vitro Drug Release

Dissolution Apparatus: USP Type I or II at 37 ± 0.5°C.

Media:

Tolbutamide/Saxagliptin: pH 6.8 phosphate buffer

Verapamil: 0.1N HCl (2 h) → pH 6.8 buffer
Sampling: Timed aliquots filtered and analyzed by UV-spectrophotometry. Results used to plot release profiles.
Development of Pellets
The development of pellet formulations for Tolbutamide, Saxagliptin, and Verapamil was strategically guided by their physicochemical properties and therapeutic objectives. Pelletization was chosen for its advantages such as uniform drug release, reduced dose dumping, ease of coating, and improved patient compliance. Two techniques were used: extrusion–spheronization for Tolbutamide and Verapamil (due to their low solubility and need for sustained release), and solution layering for the more soluble Saxagliptin. For extrusion–spheronization, HPMC served as the matrix polymer, PVP K30 as the binder, and MCC as a spheronization aid. Saxagliptin was layered onto nonpareil seeds using an HPMC-based solution and optionally coated with Eudragit RS 100 for controlled release.
A 3^2 factorial design was used to optimize polymer (5%, 10%, 15%) and binder (2%, 4%, 6%) concentrations, resulting in nine batches (F1–F9) per drug. Formulations were evaluated for pellet size, shape, drug content, flowability, and *in vitro* release. For Verapamil, optional enteric coating with Eudragit L100 or S100 provided pH-dependent release. This systematic approach using DoE ensured robust, reproducible formulations tailored to each drug's therapeutic needs.

RESULTS AND DISCUSSION
Drug-Excipient Compatibility Studies
Differential Scanning Calorimetry (DSC)

Table 4: Verapamil Pellets composition

Batch	Polymer (%)	Binder (%)	Drug Content (%)
F1	5	2	97.6
F2	5	4	99.1
F3	5	6	100.5
F4	10	2	98.8
F5	10	4	99.3
F6	10	6	101.2
F7	15	2	96.9
F8	15	4	98.4
F9	15	6	97.5

The primary objective of DSC analysis was to evaluate the thermal behavior and compatibility between Tolbutamide, Saxagliptin, Verapamil, and excipients.
*Pure Drug Thermograms:*Tolbutamide: Sharp endothermic peak at ~129–133°C, indicating melting point.
Saxagliptin: Defined endothermic peak at ~104–106°C.
Verapamil: Endothermic peak at ~145–150°C.
These peaks confirm the crystalline nature and purity of the drugs.
Drug-Excipients Physical Mixtures (1:1): No significant peak shift or change in shape: Indicates good compatibility. Slight peak shifts or broadening: Attributed to dilution or minor heat capacity changes; not indicative of incompatibility.
Major shifts, disappearance, or new peaks: Suggest interactions like eutectic formation, amorphization, or possible chemical reactions.
But drug-excipient combinations that show peak disappearance, big changes, or new transitions need to be looked at more closely. These results are important for helping you choose the right excipient, making sure the

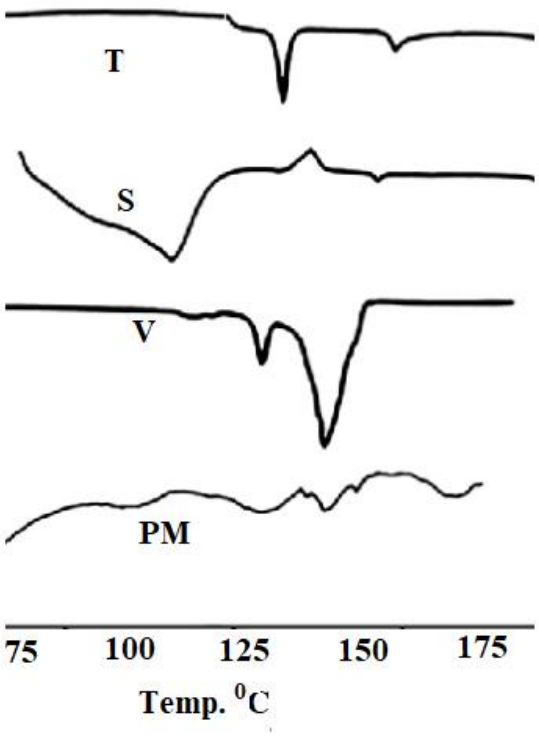

Figure 1: DSC Analysis

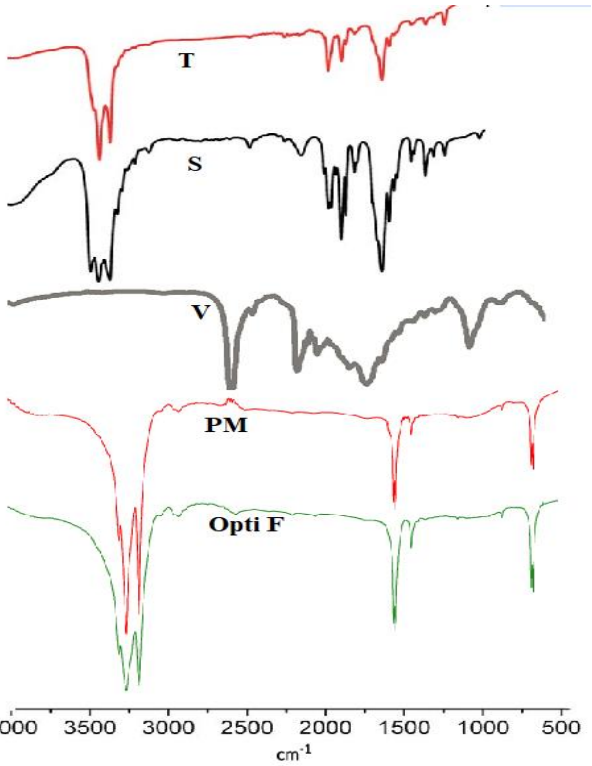

Figure 2: FTIR Analysis

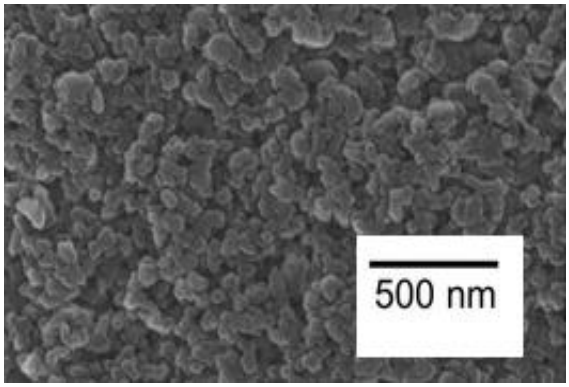

Figure 3: SEM of Optimized Batch

formulation stays stable, and figuring out how long the final product will last.

Fourier Transform Infrared Spectroscopy (FTIR)

We used FTIR to look for possible chemical interactions between the drugs (Tolbutamide, Saxagliptin, and Verapamil) and the formulation excipients by comparing the spectra of pure components with those of their 1:1 physical mixtures. Each drug had its own unique peaks that matched the functional groups it contained. Around 1150–1350 cm^{-1}, tolbutamide had strong sulfonyl group peaks. Around 1650 cm^{-1}, it had amide-related C=O stretching, around 3300–3400 cm^{-1}, it had N–H stretching, and around 1600 and 700–900 cm^{-1}, it had aromatic ring vibrations. Saxagliptin had peaks for its amide and secondary amine groups (around 1650 and 3200–3400 cm^{-1}), as well as C–C stretches related to the cyclopropyl ring (around 1000–1200 cm^{-1}). Verapamil showed ester C=O stretching between 1730 and 1750 cm^{-1}, aromatic ring stretching at about 1600 cm^{-1}, and tertiary amine bands between 2800 and 2950 cm^{-1}. When we compared the FTIR spectra of the physical mixtures to those of the pure drugs and excipients, we saw that the characteristic peaks stayed the same and there were no major shifts. This showed that there were no chemical interactions, which confirmed compatibility. In some cases,

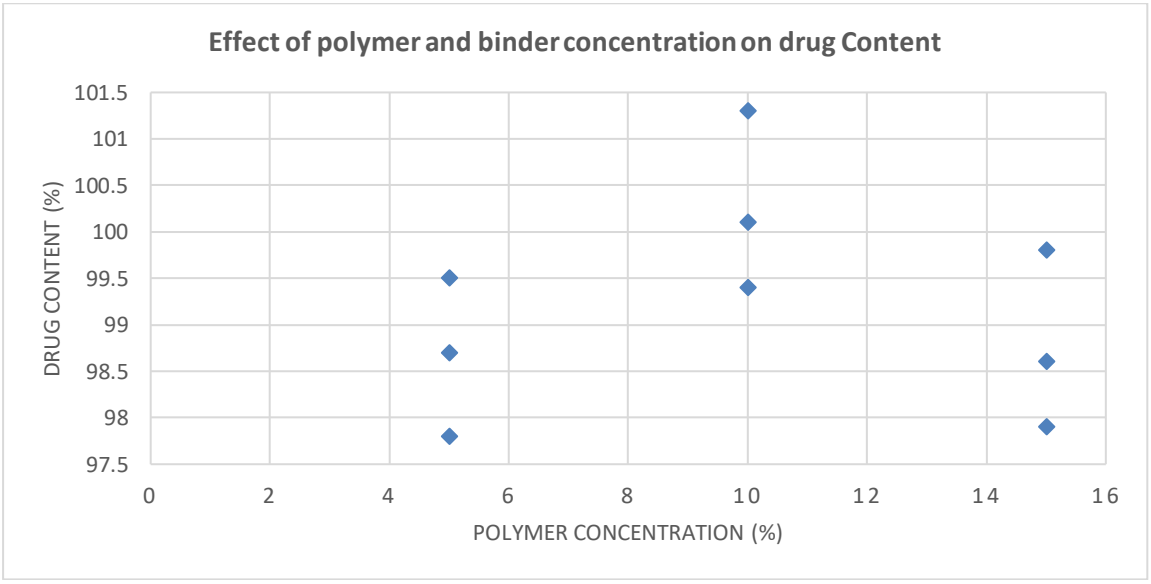

Figure 4: Tolbutamide Pellets Composition

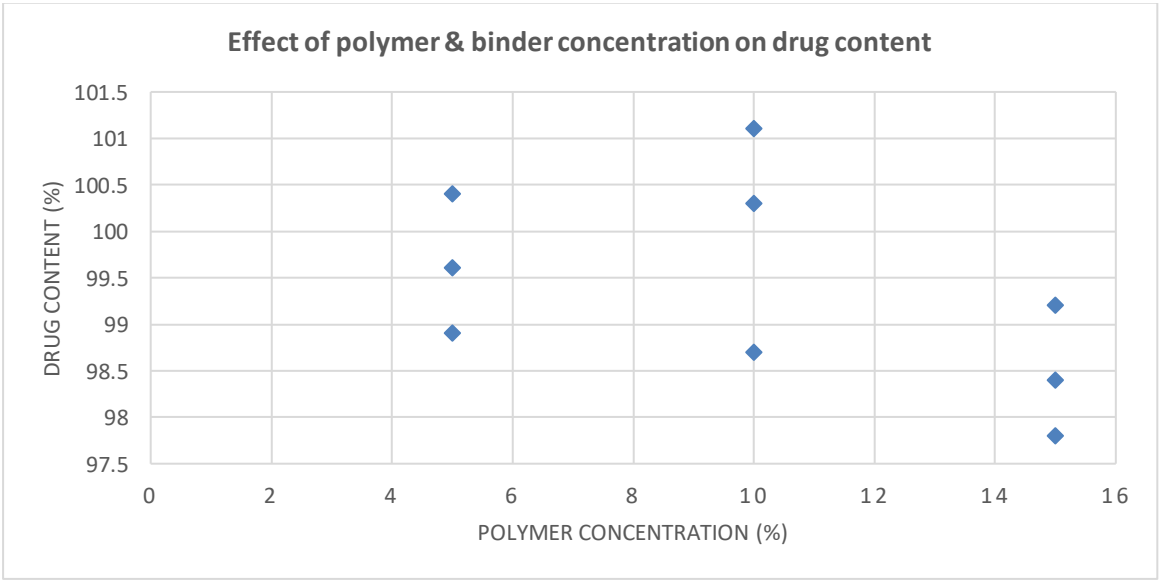

Figure 5: Saxagliptin Pellets Composition

there were small changes or broadening of peaks, which were probably caused by physical mixing or hydrogen bonding.

These changes did not mean that the two things were incompatible. But if any major peaks disappear or move a lot, it could mean that chemicals are interacting or forming complexes, which could affect the stability and effectiveness of the drug. The FTIR analysis showed that the drugs and most of the excipients used in the formulation worked well together..

Evaluation of Pellets

Flow Properties

The angle of repose test was conducted to evaluate the flowability of pellet batches F1–F9, which is essential for efficient handling during manufacturing. The measured angles ranged from 24.9° to 29.6°, indicating excellent to good flow properties. Batches with higher polymer (10–15%) and moderate binder (2–4%) concentrations—such as F4, F5, F7, and F8—showed superior flowability (<26.5°), likely due to improved sphericity and smoother surfaces.

Bulk and tapped density measurements further supported these findings. Bulk densities ranged from 0.52–0.60 g/mL and tapped densities from 0.60–0.68 g/mL. Carr's Index values (11.7%–15.6%) and Hausner Ratios (1.13–1.18) indicated good to excellent flowability across all batches, with F3 slightly higher but still within acceptable limits.

Overall, all formulations demonstrated robust flow characteristics without the need for flow aids, confirming the suitability of the compositions and processing methods for efficient manufacturing and scale-up[13].

Particle Size Analysis

Sieve Analysis

Sieve analysis was used to assess particle size distribution of pellet batches F1–F9. Using standard sieves (1000–355 µm), most pellets were retained between the 850 µm and 500 µm sieves, indicating a narrow and uniform size distribution. The mean particle sizes (D_{50}) ranged from

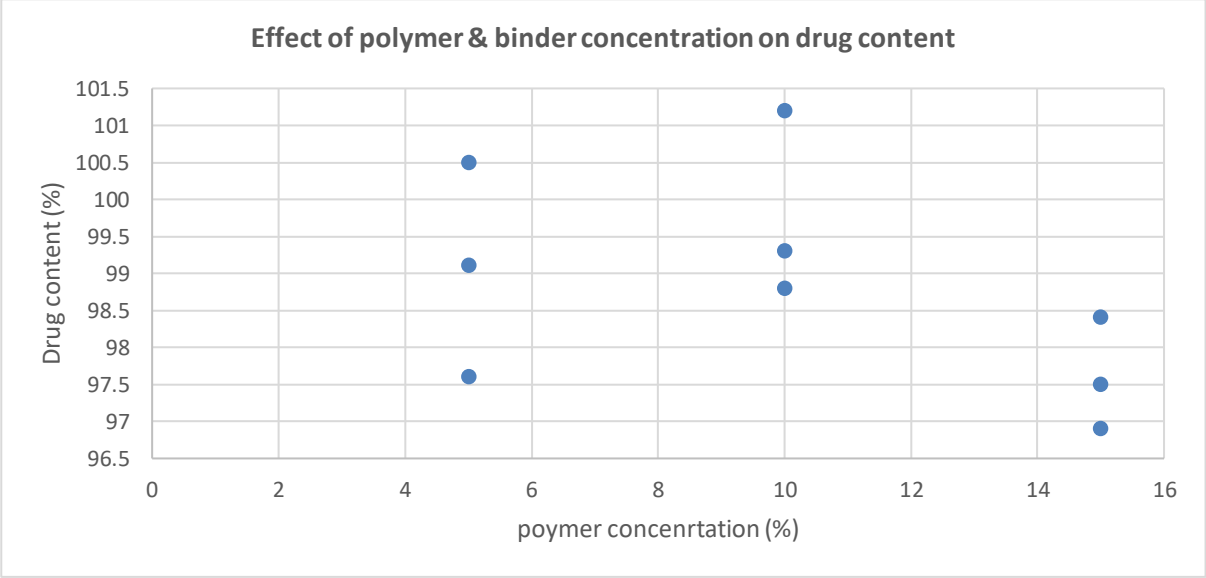

Figure 6: Verapamil Pellets composition

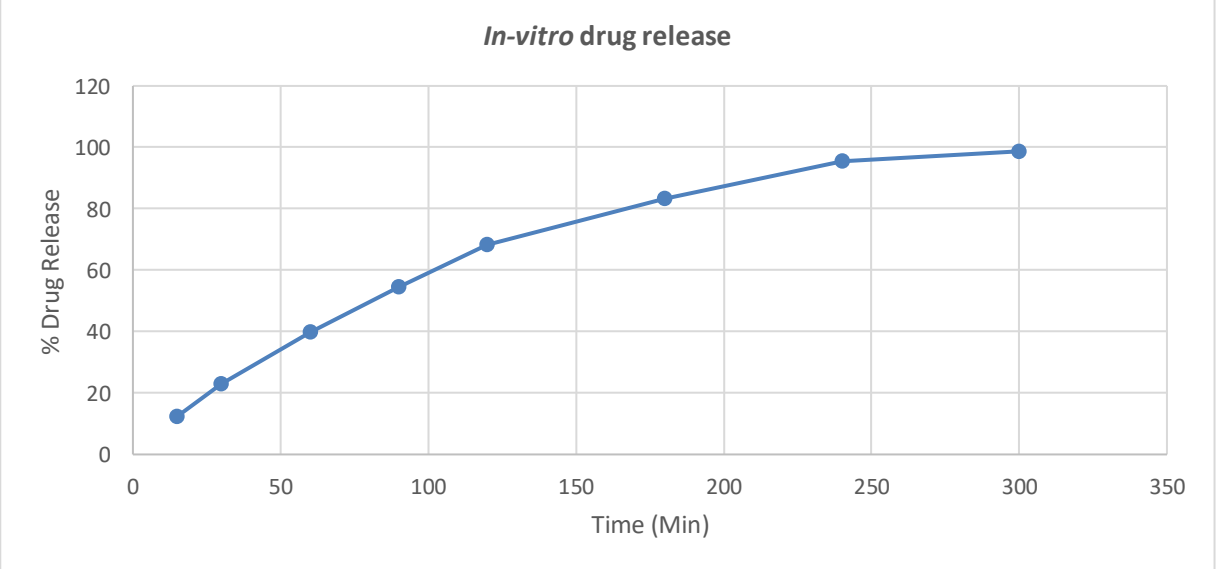

Figure 7: Cumulative % Drug Release (Optimized Batch F5)

600–720 µm, with batches F4, F5, F7, and F8 showing slightly larger sizes (~700–720 µm) due to higher polymer content enhancing matrix strength. Batches F1–F3 had smaller D_{50} values (~600–650 µm), likely from lower polymer and higher friability.

Over 85–90% of pellets in all batches fell within the desired 500–850 µm range, with minimal fines (<5%), reflecting well-controlled pelletization. This size consistency supports uniform flow, reproducible drug release, and suitability for downstream processes like coating and encapsulation.

Laser Diffraction

Also applied laser diffraction analysis to get an exact picture of the particle size distribution in pellet batches F1–F9. Depending on their composition, pellets were either dry-dispersed or put in a medium that didn't dissolve them. They were then analyzed with a laser diffraction analyzer, which gave D10, D50, and D90 values.

D50 values were between 610 and 720 µm, which is in line with sieve analysis data. Batches with higher polymer content (e.g., F4, F7) showed larger D50 (~715–720 µm), while batches with lower binder/polymer content (e.g., F1, F2) had smaller D50 (~620 µm). The D10 and D90 values were 480–580 µm and 780–850 µm, respectively, which means that the size distribution was narrow and even, and there was low polydispersity.

These results show that the pellets are consistently formed across batches, and the fact that they are all the same size is good for coating, drug release, and downstream processing. The results also show that the factorial design works well for finding the best formulation parameters.

Morphology

Scanning Electron Microscopy (SEM)

SEM was used to inspect the surface morphology of pellets from batches F1–F9. Samples were mounted on aluminum stubs, gold-coated, and imaged at magnifications ranging from 50× to 1000×.

SEM revealed that all batches produced uniformly spherical pellets with smooth surfaces, confirming efficient

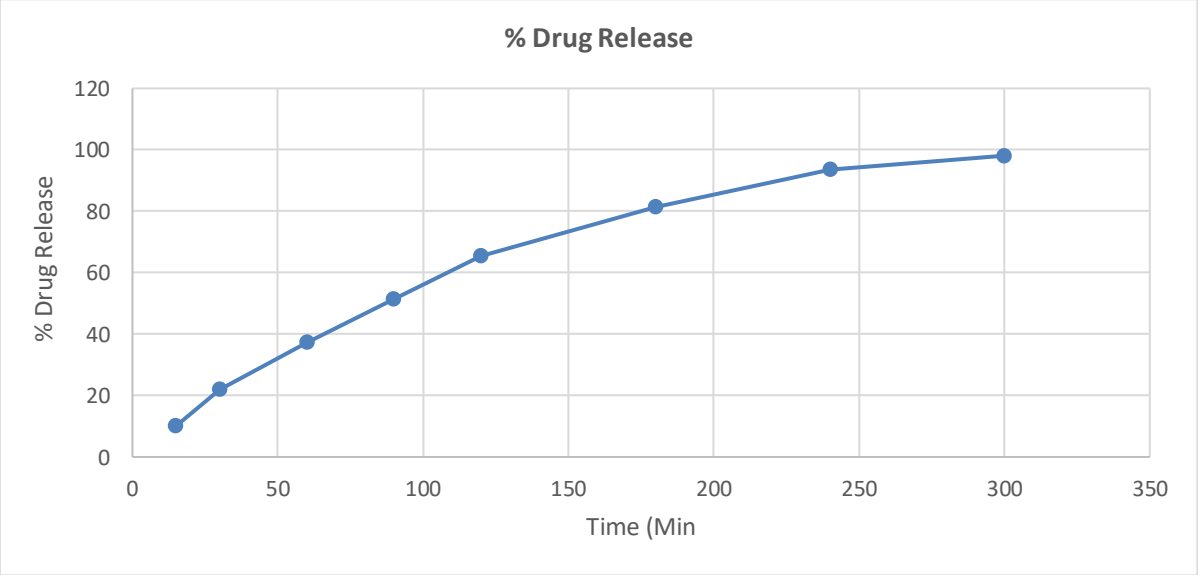

Figure 8: Cumulative % Drug Release (Optimized Batch F5)

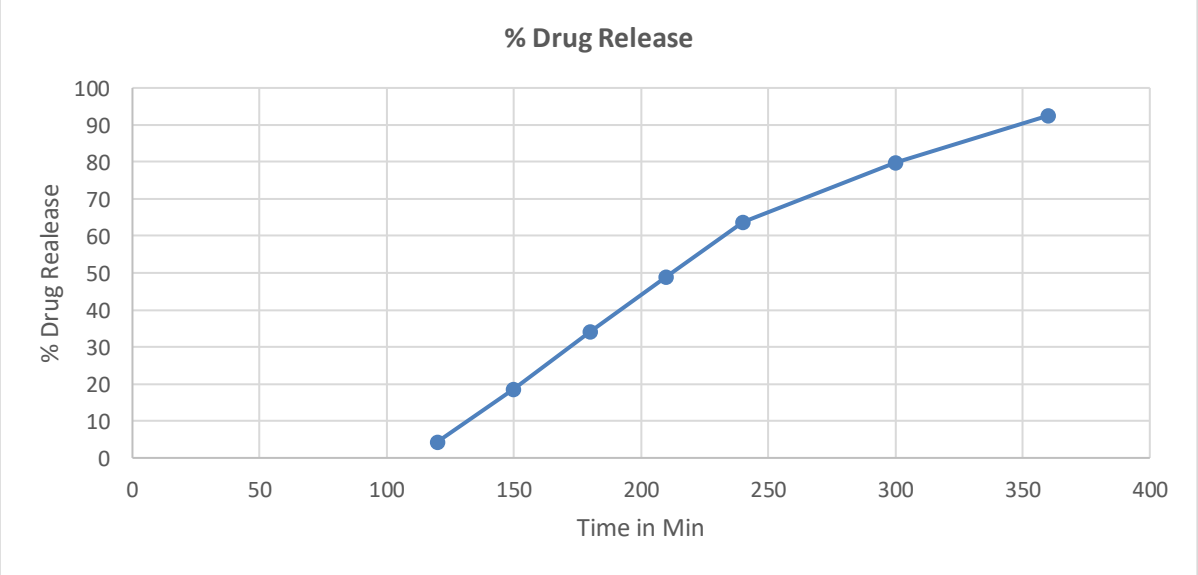

Figure 9: Cumulative % Drug Release (Optimized Batch F5)

Table 5: Cumulative % Drug Release (Optimized Batch F5)

Time (min)	% Drug Release
15	12.4
30	22.8
60	39.7
90	54.6
120	68.3
180	83.2
240	95.6
300	98.7

extrusion–spheronization and layering. Tolbutamide and Verapamil pellets showed slight surface roughness and porosity due to MCC and HPMC use. Batches with higher polymer content (F4, F5, F7, F8) exhibited denser, more compact surfaces, indicating better mechanical strength and sustained-release potential.

SEM analysis of Saxagliptin pellets (prepared via solution layering) showed smooth, uniform surfaces with thin, consistent coatings. The nonpareil cores ensured structural stability, and HPMC–Eudragit coatings were evenly applied without cracks or defects, indicating controlled fluidized bed processing. Pellets maintained high sphericity, supporting excellent flow and minimal friction—aligning with angle of repose and density data.

No major defects were observed, though minor surface irregularities appeared in lower binder batches (F1, F2), likely due to reduced plasticity. These did not affect pellet performance. Overall, SEM confirmed uniform size, good sphericity, and suitable surface features, validating the effectiveness of both extrusion–spheronization and solution layering for producing high-quality pellets.

Friability

The friability values for batches F1–F9 ranged from 0.60% to 0.92%, all well below the 1% threshold, confirming good mechanical integrity. Batches with higher polymer content (F4–F9) showed lower friability (0.60%–0.76%), likely due to improved matrix cohesiveness from HPMC and PVP K30. In contrast, F1–F3, with lower polymer levels (5%), exhibited slightly higher friability (0.83%–0.92%) but remained within acceptable limits. These results indicate that all formulations produced physically robust pellets, suitable for coating, encapsulation, and further processing without significant risk of degradation.

Drug Content Uniformity

Drug content uniformity of the formulated pellets (F1–F9) was assessed using a validated UV-Visible spectrophotometric method. Pellets equivalent to one dosage unit were randomly sampled, accurately weighed, and extracted using suitable solvents based on drug solubility (e.g., methanol or phosphate buffer for Tolbutamide). After sonication and filtration, the samples were diluted and analyzed at each drug's λmax (Tolbutamide ~230 nm, Saxagliptin ~205 nm, Verapamil ~278 nm). Concentrations were calculated using validated calibration curves, and mean drug content with %RSD was determined for each batch.

Table 6: Cumulative % Drug Release (Optimized Batch F5)

Time (min)	% Drug Release
15	10.1
30	21.9
60	37.2
90	51.5
120	65.4
180	81.3
240	93.6
300	98.1

Table 7: Cumulative % Drug Release (Optimized Batch F5)

Time (min)	% Drug Release
0–120 min (0.1N HCl)	<5%
150	18.6
180	34.2
210	48.9
240	63.7
300	79.8
360	92.5

For Tolbutamide pellets (sustained release, extrusion–spheronization), consistent drug content and low %RSD confirmed uniform distribution within the batches.

All batches for Tolbutamide, Saxagliptin, and Verapamil pellets demonstrated acceptable drug content values within the pharmacopeial specification of 85–115%, with RSD values below 2%, indicating excellent uniformity and process control. The factorial design helped optimize polymer and binder concentrations effectively across the different drugs and pelletization techniques.

In vitro Drug Release Studies

Tolbutamide Pellets (Sustained Release)

The Tolbutamide pellets demonstrated a sustained release profile, with approximately 98.7% drug released over 5 hours. This indicates effective matrix formation by HPMC and MCC, which controlled drug diffusion. The release kinetics best fit the Higuchi model ($R^2 > 0.98$), suggesting a diffusion-controlled mechanism. The Korsmeyer–Peppas model showed an "n" value between 0.45 and 0.89, indicating anomalous (non-Fickian) transport, where both diffusion and erosion play roles in release.

Saxagliptin Pellets (Controlled Release)

Saxagliptin pellets displayed controlled release behavior, attributed to the solution layering approach with HPMC and optional Eudragit RS 100 coating. The release was consistent and gradual, with more than 98% released over 5 hours. The zero-order model (R^2 ~0.96–0.98) showed the best fit, indicating a constant release rate, which is desirable for maintaining steady plasma drug levels in diabetic patients.

Verapamil Pellets (Gastro-Resistant, Sustained Release)

Verapamil pellets showed minimal release (<5%) in acidic medium, confirming the enteric coating's integrity. Upon pH shift to 6.8, sustained release followed first-order kinetics ($R^2 > 0.97$), indicating concentration-dependent release—ideal for once-daily antihypertensive therapy by

preventing gastric dose dumping. All pellets exhibited controlled or sustained release aligned with therapeutic goals. Release kinetics were: Tolbutamide—Higuchi/Peppas (diffusion and erosion), Saxagliptin—zero-order (constant rate), and Verapamil—first-order (pH-sensitive sustained). HPMC and PVP K30 effectively modulated drug release, and pelletization methods (extrusion–spheronization, solution layering) successfully achieved the desired profiles[14,15].

CONCLUSION

The present study successfully demonstrated the formulation, characterization, and evaluation of sustained and controlled release pellet systems for three therapeutically important drugs: Tolbutamide, Saxagliptin, and Verapamil. Using appropriate pelletization techniques—extrusion–spheronization for Tolbutamide and Verapamil, and solution layering for Saxagliptin—pellets with desirable physicochemical properties, uniformity, and reproducible release profiles were developed. Drug–excipient compatibility was confirmed through DSC and FTIR studies, which indicated minimal or no significant interactions between the drugs and excipients. The optimized formulations exhibited excellent flow properties, narrow particle size distribution (500–850 µm), and robust morphology as evidenced by SEM analysis. Drug content across all batches met pharmacopeial specifications, confirming uniform drug incorporation.

In vitro drug release studies revealed that: Tolbutamide pellets achieved sustained release governed primarily by a diffusion-controlled Higuchi model. Saxagliptin pellets followed a zero-order release profile, ensuring consistent plasma drug levels. Verapamil pellets exhibited pH-dependent release with minimal gastric dissolution and sustained intestinal delivery, aligning with a first-order kinetic model. These findings underscore the potential of matrix-forming and coating polymers like HPMC, PVP K30, and Eudragit variants in designing oral pellet systems tailored for specific therapeutic objectives. The employed techniques offer scalability, reproducibility, and formulation flexibility, making them viable for commercial production. Overall, the developed pellets present promising candidates for enhancing patient compliance and optimizing pharmacological outcomes in the management of diabetes and hypertension.

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