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Investigation of Dissolution Failures of Metformin Delayed-Release Tablets During Formulation Design

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ABSTRACT

Introduction: Metformin HCl (MET) is widely used as an oral hypoglycemic agent for the management of type 2 diabetes mellitus. MET is contraindicated for renal compromised patients, so low-dose formulations are recommended for renal failure patients. The alternative approach is to minimize systemic exposure without compromising the therapeutic efficacy using novel site-targeted delayed-release (DR) MET tablets with low bioavailability. Proof-of-concept studies were conducted to achieve the desired targeted dissolution profile. The manufactured batches failed to attain the desired targeted drug release profile in both acidic as well as buffer media. **Methods:** MET DR tablets were manufactured using the wet granulation method and subjected to pharmaceutical characterization. The investigation of the dissolution failures was conducted using different orthogonal analytical techniques including Fourier transform-infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and rheological studies. **Results:** DSC results revealed reduction in enthalpy values of the drug/polymer physical mixtures and subsequent change in peak transition time of a melting endothermic event. The rheological study results confirmed the loss of viscosity of the rate-controlling polymer in the presence of the drug. There could be a possible interaction between the free acid functional group of the polymer and cationic group of MET. **Conclusion:** Thermal and rheological analyses were useful analytical tools for investigating dissolution failures during formulation design, submission, and post-approval commercial manufacturing.

KEYWORDS: Metformin, diabetes, kidney failure, delayed release, tablets, dissolution

INTRODUCTION

Metformin HCl (MET) is the first-line agent for management of type 2 diabetes mellitus (T2DM), and it has been used for many decades (*1*). It gained approval from the United States Food and Drug Administration (US FDA) in 1994 and remains the most frequently prescribed medication, owing to its favorable risk-benefit ratio (*2*). MET was thought to exert its pharmacological effects by inhibiting hepatic gluconeogenesis and reducing glucose absorption from the intestine. Additionally, it enhances insulin sensitivity by promoting glucose uptake and utilization in peripheral tissues. The key benefits of MET therapy include its affordability, absence of weight gain and hypoglycemia, and reductions in triglycerides and low-density lipoprotein (LDL) levels (*3*).

MET therapy can be started with a low dose of 500 mg twice daily, and the maximum daily dose should not exceed 2000 mg. The marketed solid dosage forms of MET are immediate-release and extended-release tablets (*4*). Even though MET is the primary medication for treating T2DM, adhering to the therapy remains a clinical bottleneck. The predominant reasons for MET noncompliance include gastrointestinal (GI) side effects, such as nausea, vomiting, abdominal discomfort, and diarrhea, as well as deficiencies in vitamin B12 and folic acid (*5, 6*).

Use of MET is limited in conditions that lead to elevated blood drug concentration, such as chronic kidney disease (CKD), liver diseases, and cardiac/respiratory insufficiency. Elevated MET levels in the bloodstream can give rise to

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a condition known as lactic acidosis; although rare, the high mortality rate is a clinical concern (*7, 8*). In those patients, the US FDA advises cautious use of MET at low doses. Before initiating therapy, the patient's glomerular filtration rate should be assessed because MET is contraindicated in those with a glomerular filtration rate below 30 mL/min/1.73 m^2; the maximum recommended dose of MET for these patients is 250–500 mg (*9*). The existing MET formulations, including immediate-release and extended-release tablets, release MET in the upper portion of the intestine, resulting in higher systemic exposure, increased GI side effects, and reduced tolerance in patients with CKD (*10*).

MET delayed-release (DR) tablets are designed to deliver the drug onto the site of action with low systemic exposure, which is suitable for patients with CKD. The design of MET DR tablets increases the drug concentration in the intestine region, so intestinal targeting of MET from DR tablets reduces systemic exposure without compromising therapeutic efficacy. MET DR tablets may offer lower bioavailability, fewer GI side effects, and increased tolerability in such patients (*10*). MET DR has been used in several clinical trials, including phase 1 and 2 studies (*11–13*). The DR formulations are designed and developed as enteric-coated tablets or multi-unit particulate systems with pH-dependent polymers (*14*). The drug release mechanism for these systems is the erosion of polymeric coating upon contact with intestinal pH (*15*). However, these drug delivery systems are classified as inconsistently highly variable dosage forms due to pharmacokinetic (PK) variability with unpredicted clinical outcomes (*16, 17*).

To address the PK variability, DR matrix tablets were designed and developed for initial proof-of-concept (POC) feasibility assessment. The POC formulations failed to attain the targeted dissolution profiles. This study aims to investigate the dissolution failures of prototype formulations using different orthogonal techniques.

METHODS

Materials

MET was purchased from Exmed Pharmaceuticals (Gujarat, India). Eudragit L 100 (EL 100) and eudragit S 100 (ES 100) were obtained from Central Drug House (P) Ltd. (Delhi, India). Carbopol 934 (CP 934) and magnesium stearate (MgS) were obtained from Sisco Research Laboratories Pvt. Ltd. (Mumbai, India). Microcrystalline cellulose (MCC) was supplied by Sigma Aldrich Chemicals Pvt. Ltd. (Bangalore, India). Aerosil 200 and isopropyl alcohol were purchased from Otto Chemie Pvt. Ltd. (Mumbai, India) and TCI Chemicals (Hyderabad, India), respectively. All other solvents and reagents were analytical grade purchased from Merck (India).

Ultraviolet Method for Estimation of Drug

Ultraviolet (UV) calibration curves for MET were generated in various media, including 0.1 N HCl, pH 6.8 phosphate buffer (PB), and water (*18*). Sample solutions were prepared through a serial dilution method using the appropriate solvents. The UV absorbance of these solutions was measured using a UV-visible spectrophotometer (model 1900i, Shimadzu, Kyoto, Japan) at 233 nm, and the designated λ_{max} and calibration curves were subsequently plotted.

Quality Target Product Profiles

Quality target product profiles (QTPPs) were synthesized for POC batches to get good physical, chemical, and microbial stability of both drug substances and drug products throughout their shelf life. Drug dissolution studies are one of the predictive tools used to understand the in-vivo drug release behavior as well as absorption of the formulations being developed. PK data and dissolution data for the drug products were obtained from the literature, and physiologically based PK models were developed for intravenous and oral formulations (*19*). The developed models were validated and convoluted to obtain the in-vitro release profile (unpublished data), which was set as the target drug profile for POC establishment.

Manufacturing of Metformin Delayed-Release (MET DR) Matrix Tablets

A 2^3-factorial design was used for the formulation of MET DR tablets. The concentration of EL 100/ES 100 (X_1), CP 934 (X_2), and MCC (X_3) were taken as independent variables. A total of 22 formulations (F1–F22) including six center batches were obtained using Microsoft Excel-based software. The composition details for all batches are provided in Table 1, and independent variables are listed in Table 2.

All MET DR matrix tablet formulations were prepared using the wet granulation technique. A total target batch size of 200 tablets was used for manufacturing of POC batches. An accurately weighed quantity of MET and other excipients were sifted through a no. 40 sieve and thoroughly mixed in a polybag for 10 min. This mixture was then wet-granulated with isopropyl alcohol as the granulating solvent. The time for granulation was 15 min, and granulating solvent was poured into the powder bed after 5 min. The obtained wet granules were milled using a mini multimill (Rimek, Karnavathi, Amdavad, India). The wet granules were passed through a no. 8 sieve and dried at 60 °C in a tray dryer (Bio SB Equipments, Kalyani, India)

Table 1. Composition of Metformin Delayed-Release Matrix Tablets

Batch	MET (mg)	EL 100 (mg)	ES 100 (mg)	CP 934 (mg)	MCC (mg)	MgS (mg)	Aerosil 200 (mg)	Total Weight (mg)
F1	600	233.33	-	233.33	133.33	6.66	3.33	1209.98
F2	600	233.33	-	233.33	0	6.66	3.33	1076.65
F3	600	166.66	-	166.66	0	6.66	3.33	943.31
F4	600	200	-	200.00	66.66	6.66	3.33	1076.65
F5	600	166.66	-	233.33	133.33	6.66	3.33	1143.31
F6	600	200	-	200.00	66.66	6.66	3.33	1076.65
F7	600	166.66	-	233.33	0	6.66	3.33	1009.98
F8	600	200	-	200.00	66.66	6.66	3.33	1076.65
F9	600	166.66	-	166.66	133.33	6.66	3.33	1076.64
F10	600	233.33	-	166.66	0	6.66	3.33	1009.98
F11	600	233.33	-	166.66	133.33	6.66	3.33	1143.31
F12	600	-	233.33	233.33	133.33	6.66	3.33	1209.98
F13	600	-	233.33	233.33	0	6.66	3.33	1076.65
F14	600	-	166.66	166.66	0	6.66	3.33	943.31
F15	600	-	200.00	200.00	66.66	6.66	3.33	1076.65
F16	600	-	166.66	233.33	133.33	6.66	3.33	1143.31
F17	600	-	200.00	200.00	66.66	6.66	3.33	1076.65
F18	600	-	166.66	233.33	0	6.66	3.33	1009.98
F19	600	-	200.00	200.00	66.66	6.66	3.33	1076.65
F20	600	-	166.66	166.66	133.33	6.66	3.33	1076.64
F21	600	-	233.33	166.66	0	6.66	3.33	1009.98
F22	600	-	233.33.	166.66	133.33	6.66	3.33	1143.31

Dash (-) indicates not applicable. MET: Metformin HCl; EL 100: eudragit L 100; ES 100: eudragit S 100; CP 934: carbopol 934; MCC: microcrystalline cellulose; MgS: magnesium stearate

for 2 h. The dried blend was passed through sieve no. 16 and lubricated with MgS and Aerosil 200. The resulting granules were compressed using an 8-station rotary tablet press (Proton Engineers, Ahmedabad, India).

Table 2. Independent Variables and Their Levels Affecting Metformin Dissolution

Variable	Level		
	+1	0	-1
EL 100/ES 100 (X_1) (mg)	233.33	200	166.66
CP 934 (X_2) (mg)	233.33	200	166.66
MCC (X_3) (mg)	133.33	66.66	0

EL 100: eudragit L 100; ES 100: eudragit S 100; CP 934: carbopol 934; MCC: microcrystalline cellulose.

Evaluation of Physical Properties

All MET DR matrix tablet formulations were evaluated for dimensions, weight variation, hardness, friability, and drug content. Weight variation and hardness were assessed using a tablet tester (Labindia, Mumbai, India), and friability testing was conducted using a Roche friabilator (Labindia). The drug content of all batches was determined using the developed UV-spectrophotometric method. All evaluation procedures for physical parameters and drug content were performed in accordance with the *Indian Pharmacopoeia* (*20*).

In-Vitro Drug Release Study

Given that MET is a pH-dependent high soluble drug, media composition, volume, and hydrodynamics have insignificant roles in establishing a biorelevant dissolution method. Two dissolution studies were carried out using a United States Pharmacopeia (USP) type 1 dissolution apparatus (Labindia).

The first dissolution test was performed in two stages (acid stage and buffer stage) with 900 mL of 0.1 N HCl and pH 6.8 PB, respectively, at 50 rpm and 37 ± 0.5 °C. Sampling occurred at 30, 60, and 120 min during the acid stage, with 5 mL samples collected and replaced with an equal volume of fresh medium to maintain sink conditions. Following the acid stage, the tablets were transferred to the buffer stage, and samples were collected at 3, 4, 6, 10, and 14 h. Collected samples were appropriately diluted and analyzed using a UV-visible spectrophotometer at λmax of 233 nm. The percentage of drug release was calculated and reported.

The second dissolution test was performed for all center point batches (F4, F6, F8, F15, F17, and F19) using pH 6.8 PB as the medium. Sampling intervals were 0.5, 1, 2, 3, 4, 5, and 6 h, and all other dissolution parameters were the same. These samples were similarly diluted as needed and assessed using a UV-visible spectrophotometer at 233 nm to determine the MET content.

Both dissolution procedures were carefully chosen based on the previous literature (*21*). The two-stage method was used to ensure the acid-resistant nature of the DR formulations as a fasting biopredictive tool. The second method was used as a quality control (QC) tool for routine current good manufacturing practices (cGMPs) in addition to the acid-resistant test stated in the pharmacopeia (*22*).

Investigation of Dissolution Failures

Dissolution failures of POC batches were investigated in the solid state as well as the solution state using different orthogonal analytical techniques. The physical composition of the drug and excipients were prepared using the reported method (*23*). Fourier transform-infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), and scanning electron microscopy (SEM) studies were performed to explore solid-state incompatibilities, and rheological studies were performed to explore solution-state incompatibilities that resulted in the dissolution failures.

Fourier Transform Infrared Spectroscopy (FT-IR)

The compatibility of MET with excipients was evaluated using FT-IR spectroscopy. MET and polymers were blended in a 3:1 ratio, resulting in various combinations: MET + EL 100, MET + ES 100, MET + CP 934, MET + CP 934 + EL 100, and MET + CP 934 + ES 100. For FT-IR analysis, each sample was divided into three portions for estimations on day 0, 15, and 30 and scanned using the FT-IR spectrometer (Spectrum Two with $LiTaO_3$ detector and UATR Two, Perkin Elmer, USA). The spectra of each sample were collected in 2-min intervals immediately after placing the sample on the diamond crystal (range of 400–4000 cm^{-1}, single scan mode, resolution of 4 cm^{-1}). A comparative analysis of all spectra was conducted to identify potential solid-state incompatibilities, focusing on principal drug peaks and presence or absence of peaks indicative of any polymer interactions.

Differential Scanning Calorimetry (DSC)

DSC studies were conducted on various samples including MET, CP 934, EL 100, ES 100, and combinations such as MET + CP 934, MET + EL 100, MET + ES 100, MET + CP 934 + EL 100, and MET + CP 934 + ES 100. The DSC instrument (DSC 2500, TA instruments, USA) consists of a finer air-cooling system, autosampler, and discover liquid nitrogen pump. Aluminium pans were used for DSC analysis (Tzero Pan model T 210503, Lot 160141; Tzero lid model T 210830, lot 170048). The samples were weighed in an aluminium pan, and the samples contained 3.0 mg equivalent of MET. DSC samples were analyzed with an analytical heating rate of 10 °C·min^{-1} at a nitrogen flow rate of 50 mL·min^{-1}. The temperature range of the experiments was kept between 25 °C and 250 °C. Differences in heat flow rate were measured against an empty pan as a reference.

Scanning Electron Microscopy (SEM)

The SEM analysis (GeminiSEM 360, ZEISS Microscopy, Jena, Germany) was performed on samples comprising individual drugs and excipients, as well as their physical mixtures. The physical mixtures included MET + EL 100, MET + ES 100, MET + CP 934, MET + CP 934 + EL 100, and MET + CP 934 + ES 100. These samples were affixed to carbon double-sided tape, subjected to gold-coating via sputtering, then analyzed using a 15-kV excitation voltage under a vacuum of 5–10 Torr.

Rheological Studies

The rheological studies characteristics of EL 100, ES 100, and CP 934 in matrix tablets and their impact on drug release were investigated using a modular compact rheometer (MCR 302e, cone plate CP40-1, Anton Paar, Hofheim, Germany) The study involved individual samples of MET, CP 934, EL 100, and ES 100, as well as their various mixtures in water and 0.1 N HCl. Viscosity was measured using a cone-plate system with a 40-mm diameter and 1° cone angle. The measurements were performed at both 25 °C and 37 °C, maintaining a constant shear rate of 20 s^{-1}. Over a duration of 0–600 s, a total of 20 measuring points were recorded to generate a viscosity versus time curve, and mean viscosity was used to evaluate the samples.

RESULTS AND DISCUSSION

The calibration curves obtained from UV-visible spectra, which were used for the quantification of the drug, are provided as supplemental material (Supplemental Figure 1).

All physical parameters were well within the acceptable regulatory limits, except drug content. Physical characteristics and drug content for all MET DR tablet formulations are also provided as supplemental material (Supplemental Table 1).

In-Vitro Drug Release Study

The target dissolution profile for the two-stage method was no more than 10% drug release in 2 h (acid stage),

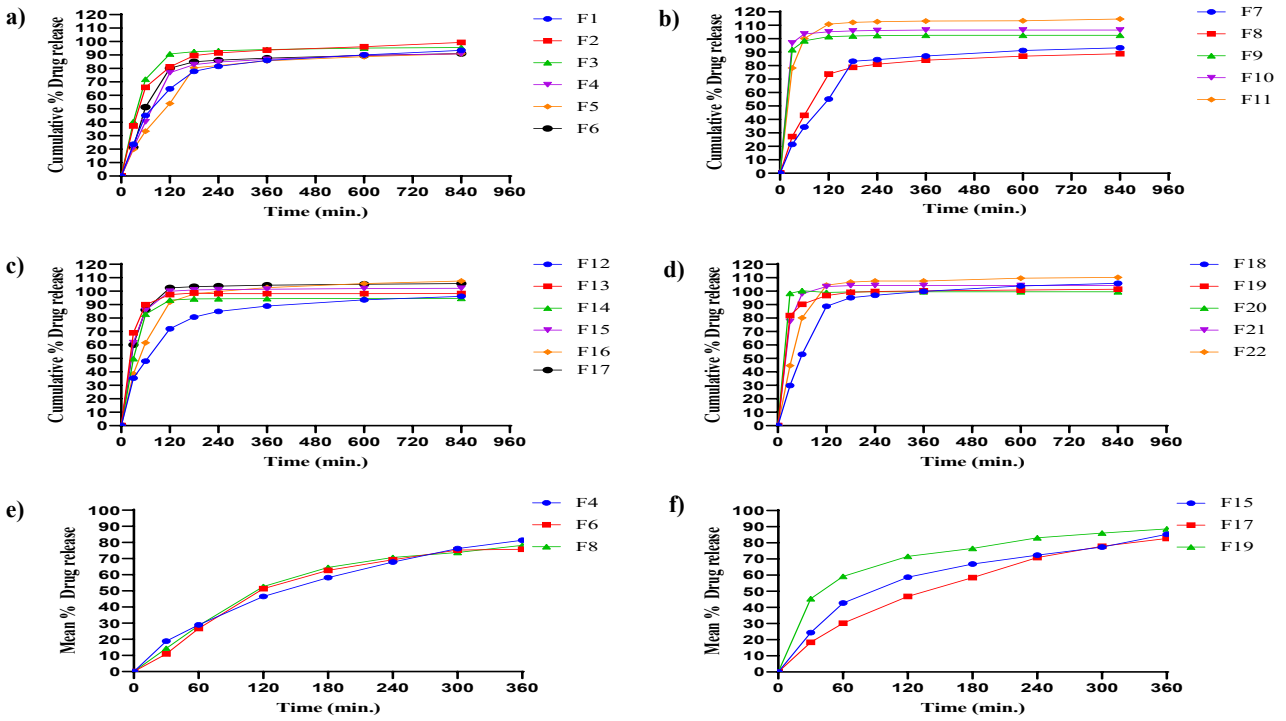

Figure 1 . Comparative in vitro dissolution profiles of Metformin delayed-release tablets; a–d: Formulations F1–F22 in acid and buffer stages; e and f: quality control batches (F4, F6, F8, F15, F17, F19) in 6.8 phosphate buffer alone.

40–60% in 3.5 h (buffer stage), and 90% in 4 h (*24*). The QC dissolution method specifications were obtained from USP (*22*). All MET DR tablet formulations were expected to exhibit no more than 10% drug release in the acid stage, followed by an immediate or controlled release in the buffer stage.

Figure 1 depicts the in-vitro drug release profiles of all batches with both dissolution methods. All batches failed to meet the target dissolution profile, exhibiting more than 10% drug release in 2 h. Specifically, batches with high concentrations of EL 100 (F10 and F11) showed 90% drug release, ES 100 showed more than 90% drug release, and high concentrations of CP 934 (F5 and F7) showed around 50% drug release in 2 h. MET is a strong base HCl salt, so the pH of the saturated solution is 6.9. This neutral pH is sufficient to form enough gelation for controlling drug release from the matrix, thus high CP 934 content in the formulation results in a slower release rate. Surprisingly, batches with EL 100 as a polymer exhibited a relatively slower release profile compared to those with ES 100.

The critical threshold pH for solubility is 6.0 and 7.0 for EL 100 and ES 100, respectively. Both EL 100 and ES 100 are anionic polymers; however, the free acid functional group is 50% for EL 100 and 33% for ES 100. In an enteric-coated system, the drug-polymer interaction is minimal due to the physical protection of seal coating. In a matrix system, the free acidic group in eudragit polymer creates the acidic microenvironment that facilitates faster drug release for basic drugs like MET. Hence, the faster drug release profile of ES 100 compared with EL 100 is due to pH of the acidic microenvironment. Moreover, the pH-dependent nature of enteric polymers results in low swelling and erosion in an acidic environment, thus resulting in poor matrix integrity. The critical dissolution pH of eudragit polymers has minimal impact on drug release. Therefore, alteration of the tablet matrix microenvironment pH should be considered when selecting rate-controlling polymers.

In the buffer stage alone (QC method), less than 50% of the drug was released within the initial 2 h. Notably, 90% drug release only occurred after 6 h, regardless of whether the batches contained EL 100 or ES 100. Differences in drug release profiles between acid-treated vs buffer-alone dissolution could be due to buffering capacity of dissolution media, which did not alter the microenvironmental pH significantly and hence had no meaningful impact on dissolution in the first 2 h. CP 934 was used as a rate-controlling polymer to control drug release in acidic conditions owing to favorable physicochemical properties such as ionization, pKa, and pH-dependent solubility (pKa of CP 934 is reported as

6.0, and an acidic polymer gets ionized and swells at a pH above 6.0). In acidic pH, these acrylic polymers are unionized and have low solubility and poor gel formation. In acidic pH, MET has relatively high solubility and CP 934 has poor gel formation, so the matrix erodes rapidly and fails to control drug release. However, in buffer-only dissolution studies, the extent of gel formation inside the matrix was relatively high due to buffering capacity, thus drug release was controlled better than in acid-stage dissolution studies.

Investigation of Dissolution Failures

FT-IR Study

Analysis of the spectra revealed that the peaks corresponding to the major functional groups of MET remained unchanged even in the presence of excipients (Table 3). This observation confirms the absence of solid-state interaction between the drug and polymers in the formulation without any physical and chemical instability issues during their shelf life. Results of the FT-IR study are provided in the supplemental material (Supplemental Figures 2–4).

Table 3. Peaks and Corresponding Functional Groups of MET HCl

Functional Group	Reported Wave Number Range	Observed Wave Number
N-H stretching	3100–3400	3370.2
N-H in-plane deformation	1530–1590	1556.97
N-H wagging	660–910	938.0
C=N stretching	1580–1685	1623.2
C-N stretching	1020–1220	1060.4
C-H	3095–3010	3146.5
CH_3 asymmetric deformation	1445–1475	1446.46

MET: metformin HCl; N: nitrogen; H: hydrogen; C: carbon.

DSC Study

DSC experiments are widely used in pre-formulation research (*25*). The DSC parameters for MET and its various formulations are detailed in Table 4, and DSC thermograms are provided in the supplemental material (Supplemental Figure 5). For MET, a peak transition temperature of 233.3 °C was recorded with an enthalpy of 324.2 J/g. The peak transition temperature decreased in all formulations, notably with the CP 934 + EL100 mixture. The enthalpy of MET for melting was significantly lower with all formulations. The CP 934 mixture had a low enthalpy value of 111.9 J/g compared with eudragit polymers. The formulation of MET with EL 100 resulted in the lowest enthalpy of 91.3 J/g. This observation agrees with results obtained from the dissolution studies. EL 100 formulations have a comparatively low extent of dissolution when compared with ES 100 formulations. This could be due to the relationship between melting enthalpy and free energy, and the associated free energy used for dissolution of the drug from the matrix.

The significant reduction in enthalpy of the granules might reveal the thermodynamic characteristics of the granules, which may be used to investigate dissolution failures during POC selection and life-cycle management.

Table 4. Parameters from DSC Thermogram Studies

Sample	Onset of MET (°C)	Peak of MET (°C)	Enthalpy of MET (J/g)
MET	231.26	233.23	324.24
MET + CP 934	228.08	231.21	111.86
MET + EL 100	224.34	231.11	194.73
MET + ES 100	229.74	232.85	161.00
MET + CP 934 + EL 100	228.20	228.84	91.27
MET + CP 934 + ES 100	226.84	231.34	98.45

DSC: differential scanning calorimetry; MET: Metformin HCl; CP 934: carbopol 934; EL 100: eudragit L 100; ES 100: eudragit S 100.

SEM Study

Figure 2 displays the photomicrographs of MET, CP 934, EL 100, ES 100, and their physical mixtures. The results indicate that both MET and the excipients maintain their distinct morphologies, with no evidence of morphological changes in the MET crystals and excipients. This observation reconfirms the solid-state stability of the physical mixtures.

Results obtained from FTIR and SEM confirmed the absence of solid-state interaction. Therefore, interactions between the drug and polymer are solution-state mediated, and the pH plays an important role in the matrix integrity.

Rheological Studies

Viscosity studies were carried out in the solution state, whereas dissolution studies were performed in saturated conditions. Swelling of the polymer during the initial stage of dissolution restricts the entry of dissolution media inside the tablet matrix core, thereby retaining the matrix integrity. Viscosity measurements are useful for the initial assessment of dissolution behavior of the formulation during the design stage and for retrospective investigation of batch failures.

Table 5 presents the viscosity values for all MET DR formulation samples. The results confirmed that the viscosity of CP 934 in 0.1 N HCl is lower than that in water. This is due to the higher degree of ionization and swelling of CP 934 in the presence of water when compared with 0.1 N HCl.

Temperature has a significant effect on the viscosity of the

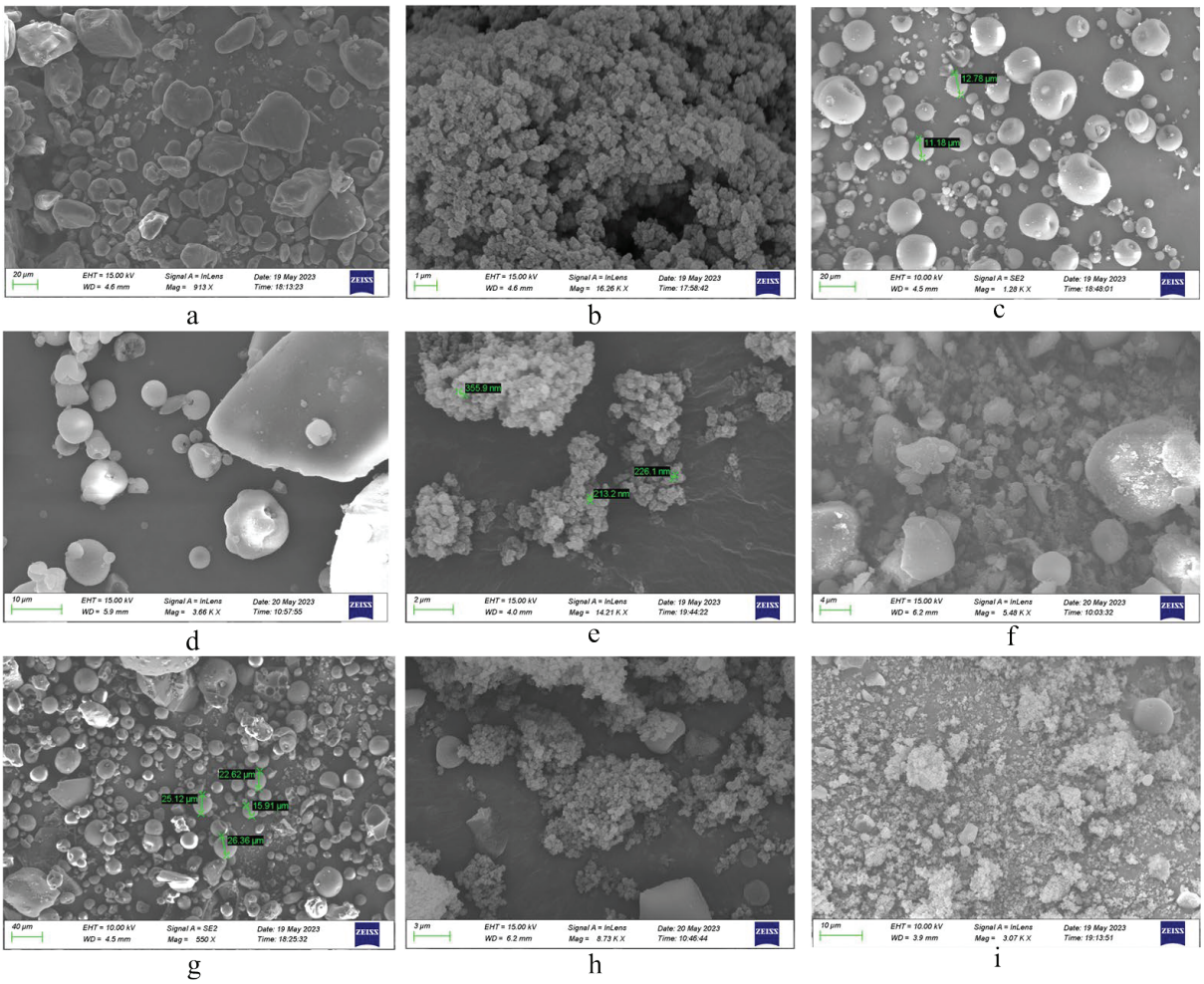

*Figure 2. Scanning electron microscopy images of Metformin delayed-release tablets; (**a**) MET, (**b**) CP 934, (**c**) EL 100, (**d**) ES 100, (**e**) MET + CP 934, (**f**) MET + EL 100, (**g**) MET + ES 100, (**h**) MET + CP 934 + EL 100, and (**i**) MET + CP 934 + ES 100.*
MET: Metformin HCl; EL 100: eudragit L 100; ES 100: eudragit S 100; CP 934: carbopol 934.

Table 5. Viscosity of MET formulations in Water and 0.1 N HCl

Sample	Viscosity (mPaS)			
	Water		0.1 N HCl	
	25 °C	37 °C	25 °C	37 °C
0.3% MET	0.9 ± 0.045	0.7 ± 0.005	0.74 ± 0.05	0.78 ± 0.05
0.3% CP 934	23.7 ± 1.6	38.0 ± 1.6	1.4 ± 0.09	3.9 ± 0.36
0.1% EL 100	0.8 ± 0.02	0.7 ± 0.05	0.82 ± 0.006	0.82 ± 0.03
0.1% ES 100	0.76 ± 0.02	0.78 ± 0.01	-	-
0.3% MET + 0.3% CP 934	1.7 ± 0.09	1.9 ± 0.07	2.4 ± 0.78	5.4 ± 1.18
0.3% MET + 0.1% EL 100	1.7 ± 0.29	1.8 ± 0.29	0.85 ± 0.04	0.72 ± 0.04
0.3% MET + 0.3% CP 934 + 0.1% EL 100	5.0 ± 0.38	4.6 ± 0.7	5.8 ± 1.25	12.9 ± 3.06
0.3% MET + 0.3% CP 934 + 0.1% ES 100	4.5 ± 0.02	3.5 ± 0.4	-	-
0.3% CP 934 + 0.1% EL 100	19.4 ± 1.5	13.5 ± 0.52	1.8 ± 0.12	4.2 ± 1.6
0.3% CP 934 + 0.1% ES 100	27.6 ± 1.16	30.03 ± 1.8	1.53 ± 0.06	1.6 ± 0.43

Values are expressed at mean ± SD.
Dash (-) indicates not applicable; MET: Metformin HCl; CP 934: Carbopol 934; EL 100: Eudragit L 100; ES 100: Eudragit S 100.

solution. The viscosity of CP 934 gel in a physiologically relevant temperature of 37 °C is higher than the ambient conditions. Although there is an insignificant difference in the pH of water vs saturated solution of MET (6.4 vs 6.9), the presence of MET has a significant reduction in the viscosity of CP 934 due to the presence of a cationic reactive functional group of MET. Hence, the use of CP 934 as a rate-limiting polymer in matrix tablets is questionable.

The data obtained from viscosity measurement of eudragit polymers revealed that there was no role of these polymers in gelation. The probable mechanism for controlling drug release could be their pH-dependent erosion pattern; however, the free acidic group might influence drug release rather than pH-dependent ionization and erosion. A key observation from this investigation was that EL 100 reduced viscosity of the CP 934 polymer, whereas ES 100 increased viscosity. Although the CP 934 + EL 100 mixture had less viscosity than the CP 934 + ES 100 mixture, the rate of dissolution was faster with ES 100 than with EL 100. This indicates that rather than viscosity, the free acid function group plays an important role in the faster dissolution profile of ES 100 compared with EL 100.

The presence of MET in the polymeric system reduced viscosity to a greater extent (i.e., 27.6 vs 4.5 cps). These data reveal that the solution-state physical interaction between the drug and excipients reduced viscosity of the polymeric formulations. This could be due to the presence of a strong cation, which interacts with the free anionic group in both eudragit and CP 934 polymers. This interaction resulted in lowering of not only viscosity but also gelation of polymer, subsequently reducing matrix integrity.

Moreover, MET has high aqueous solubility and ionization. The solubility of MET is high in acidic pH, which favors dissolution. The presence of free acidic functional groups and their influence on microenvironmental matrix pH further enhances the solubility of MET in a matrix, hence causing the observed dissolution failures in DR tablets.

CONCLUSION

This study aimed to investigate observed dissolution failures of POC batches of MET DR tablets. DSC studies revealed a difference in peak endothermic transition temperature and associated enthalpy, indicating a possible interaction between the drug and polymers, which may have caused dissolution failure. Polymers such as CP 934, EL 100, and ES 100 have free acidic functional groups that interact with MET in the solution state, resulting in lower enthalpy values, which may be linked with higher free energy for solubilization and lack of controlled drug release. Rheological studies revealed reduced viscosity of these polymers in the presence of MET, indicating failure to provide sufficient gel strength to control the release profile. This study demonstrated that DSC and rheological studies are useful for the investigation of dissolution failures in design stage optimization as well as commercial manufacturing.

SUPPLEMENTAL MATERIAL

Supplemental material is available for this article and may be requested by contacting the corresponding author.

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DISCLOSURES

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