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Effects of Formulation Composition and Manufacturing Processes on the In Vitro Dissolution Profile of Estazolam Tablets

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ABSTRACT

Background: Estazolam (EZ) is a benzodiazepine-class medication prescribed for the treatment of insomnia and for use in preoperative anesthesia. This investigation aimed to comparatively analyze the in vitro dissolution profiles of generic EZ tablets from 12 manufacturers in China and the innovator drug to identify how variations in the formulation composition, manufacturing process, and microstructure affect their dissolution characteristics. **Methods:** Dissolution testing was performed using the paddle method (50 rpm) in four media: hydrochloric acid (HCl) (pH 1.2), acetate buffer (pH 4.0), phosphate buffer (pH 6.8), and water. The similarity factor (f_2) was used to assess the similarity between the dissolution profiles of the generic EZ tablets and the innovator drug. Properties of the active pharmaceutical ingredients (APIs), formulation compositions, manufacturing processes, and microstructural characteristics of the generic EZ tablets and the innovator drug were comparatively analyzed. **Results:** Four of the 12 manufacturers conducted and passed the consistency evaluation tests and achieved dissolution greater than 85% within 15 min across all media, demonstrating superior intra- and inter-batch consistency (M1–M4). Their dissolution profiles closely matched that of the innovator drug. Six of the eight manufacturers who did not conduct consistency evaluations exhibited inadequate inter-batch uniformity, reduced dissolution rates, and divergent profiles, indicating potential differences in therapeutic efficacy compared with the innovator. Formulation analysis identified that lactose content and the uniformity of API dispersion within excipients are the key determinants of dissolution performance. **Conclusion:** Generic EZ tablets from manufacturers who conducted and met the consistency evaluation standards demonstrated superior quality, having dissolution characteristics comparable to those of the innovator drug, whereas tablets from manufacturers who did not conduct consistency evaluation tests require optimization of the lactose content and API-excipient blending processes to for optimizing their dissolution profiles. This study provides valuable insights for improving the formulations and manufacturing processes of drugs to meet the requirements of consistency evaluation tests.

Keywords: Estazolam tablets, generic drugs, consistency evaluation, quality, efficacy, dissolution behavior, formulation, manufacturing process

INTRODUCTION

Estazolam (EZ) is a benzodiazepine medication classified as a class II psychotropic substance in China (*1*, *2*). EZ is primarily indicated for the treatment of insomnia and for use in preoperative anesthesia, with widespread application in clinical practice (*3*, *4*).

EZ exhibits poor water solubility and is classified as a class I drug according to the Biopharmaceutics Classification System (BCS), and a Class II drug according to the Biopharmaceutics Drug Disposition Classification System (BDDCS) (*5*–*7*). This classification indicates that EZ has low solubility, high permeability, and extensive metabolism. The discrepancy between BCS and BDDCS classifications appears to be primarily dose-dependent. For poorly soluble drugs, the crystal form and particle size of the active pharmaceutical ingredients (APIs) can influence the dissolution rate, solubility, and bioavailability of the formulation.

EZ tablets were initially approved for marketing in Japan in April 1975 under the trade name EURODIN, available in 1- and 2-mg strengths. Consistency evaluation tests are conducted to assess the uniformity of quality in marketed generic drugs across different phases and batches, to ensure that their quality and efficacy are equivalent to those of the innovator drug. In China, 12 manufacturers produce generic EZ tablets (all are 1-mg strength). The formulation and process documentation provided by the manufacturers indicates that the formulation compositions of the tablets sourced from four of these manufacturers closely aligns with that of the innovator drug, and the other formulations have compositional variations.

Few studies have investigated the methods used to determine the dissolution of EZ tablets. The *United States Pharmacopeia* (USP) monograph and *Japanese Orange Book* specify procedures for determining the dissolution profile of tablet formulations (*8*, *9*). However, the relationship between the in vitro dissolution profile of EZ tablets and their formulation or manufacturing processes remains to be investigated.

This study aimed to compare the dissolution profiles of generic EZ tablets produced by 12 Chinese pharmaceutical manufacturers with that of the innovator drug. The similarities between the dissolution profiles of the generic tablets and the original drug were evaluated using similarity factor (f_2) analysis, and the key factors affecting the intrinsic quality differences were further analyzed. The findings provide valuable guidance for the formulation and process development of generic EZ drugs to ensure that they meet the quality and efficacy standards comparable to those of the innovator drug.

METHODS

Samples, Chemicals, and Reagents

Potassium dihydrogen phosphate, anhydrous disodium hydrogen phosphate, sodium acetate, hydrochloric acid (HCl), and glacial acetic acid were purchased from Chongqing Chuandong Chemical Co. Ltd. (Chongqing, China). High-performance liquid chromatography (HPLC)-grade acetonitrile was procured from Anhui Shilian Special Solution Co. Ltd. (Anhui, China) for sample analyses. Ultrapure water was produced in the laboratory. Two batches of the innovator drug (lot nos. AA1624 and AA1625) were obtained from Teva Takeda Yakuhin Ltd.

(Japan). The EZ reference substance (lot no. 171219-201604; purity 99.9%) was purchased from China Food and Drug Testing and Research Institute (Beijing, China). The 12 manufacturers were identified numerically as M1–M12. Tablet manufacturers 1, 3, and 4, and one additional company (M13) were identified as the API manufacturers. Product information for all 12 generic drug manufacturers is presented in Table 1.

Table 1. Product Information for Generic Estazolam Tablets

Manufacturer	Batch No.	Expiry Date	Marketing Authorization Holder
M1	20221018	2024/10	Changzhou Siyao Pharmaceuticals Co. Ltd.
M2	65221101	2024/10	SPH Sine Pharmaceutical Laboratories Co. Ltd.
M3	220101	2024/12	Shandong XinYi Pharmaceutical Co. Ltd.
M4	20220902	2026/08	Huazhong Pharmaceutical Co. Ltd.
M5	2202064	2025/01	Chifeng Mysun Pharmaceutical Co. Ltd.
M6	C2211291	2025/10	Xinxiang Changle Pharmaceutical Co. Ltd.
M7	220404	2025/03	Beijing Haiwang Zhongxin Pharmaceutical Co. Ltd.
M8	44221243	2024/12	CSPC Pharmaceutical Holdings Group Co. Ltd.
M9	20221203	2026/12	Beijing Yimin Pharmaceutical Co. Ltd
M10	220301	2024/02	Guangdong Nanguo Pharmaceutical Co. Ltd.
M11	B2211061	2025/10	Hunan Dongting Pharmaceutical Co. Ltd.
M12	221001	2024/10	Jinan Yongning Pharmaceutical Co. Ltd.
M13	202302001	2025/02	*Shanxi Shuangyan Pharmaceutical Co. Ltd.*

Qualification, Verification, and Calibration

All dissolution apparatus were subjected to mechanical qualification, verification, and calibration to ensure compliance with the regulatory requirements. An accredited third-party institution conducts annual mechanical qualification and verification, and the instrument managers perform semi-annual calibration using salicylic acid tablets to support performance qualification.

The specificity, linearity, precision, accuracy, room temperature stability, and robustness of the HPLC method used to determine the dissolution of EZ tablets in four different media (water, HCl [pH 1.2], acetate buffer [pH 4.0], and phosphate buffer [pH 6.8]) were validated in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline Q2(R1) (*10*). The results confirmed that the established chromatographic conditions were suitable for determining the dissolution of EZ tablets in the four media.

- Specificity analysis confirmed that the blank solvent and excipients did not produce any interference.
- Linearity was established over the concentration range of 0.1134–2.2677 µg/mL for the four media: water (y = 5.0957x – 0.0149; r = 1.0000), HCl (Y = 2.3119x + 0.0208; r = 1.0000), acetate buffer (y = 4.9531x – 0.0042; r = 1.0000), and phosphate buffer (y = 5.2254x – 0.0147; r = 1.0000).

- Precision analysis yielded relative standard deviation (RSD) values of 0.1% for water, HCl, and phosphate buffer (n = 6), and 1.0% for acetate buffer.
- Accuracy studies revealed that the mean (RSD) recoveries for water, HCl, acetate buffer, and phosphate buffer were 99.2% (0.8%), 100.4% (0.5%), 100.2% (1.2%), and 99.7% (0.8%) across three concentration levels (10%, 100%, and 150%; n = 9).
- Room temperature testing confirmed the stability of the samples for at least 24 hours.
- Robustness testing under modified chromatographic conditions produced a mean (RSD) labeled content of 96.3% (0.5%), thus validating the reliability of the method. EZ showed no membrane adsorption in any of the four media.

Dissolution Test

The dissolution test was performed using the paddle method with a fully automatic UDT-814 dissolution tester (Distek, USA) at 50 rpm and using four different dissolution media (900 mL) at different pH levels: HCl (pH 1.2), acetate buffer (pH 4.0), phosphate buffer (pH 6.8), and water, according to the *USP* monograph and *Japanese Orange Book* (*8*, *9*).

The dissolution profiles were determined according to the second of the four general methods outlined in *The Pharmacopoeia of the People's Republic of China* (*Ch.P*) (*11*). A filter head located at the sampling end of the automated dissolution tester enables filtering. Samples were collected at 5, 10, 15, 30, 45, 60, 90, and 120 min. A 2-mL sample was collected without media replenishment and subsequently transferred from test tubes to autosampler vials.

The dissolution of EZ tables was measured via HPLC (Thermo Fisher Vanquish Core, USA). HPLC analysis was performed using octadecylsilane-bonded silica gel as the stationary phase, and a mobile phase of acetonitrile-water (40:60, v/v). Detection was performed at a wavelength of 223 nm. The temperature of the column was maintained at 30°C, and a 50 µL injection volume was used for each sample. The tablet formulation was considered to meet the required criterion if more than 80% of the labeled amount (Q) dissolved within the specified timeframe (***Error! Reference source not found.***).

Moisture Content

The moisture content of EZ tablets was assessed using a moisture analyzer (METTLER TOLEDO, Switzerland), according to *Ch.P* General Rule 0832 Method 1 (Karl Fischer Method) (*11*).

API Crystal Forms and Particle Size

X-ray diffraction (XRD) was analyzed using an x-ray diffractometer (Rigaku, Japan), according to *Ch.P* General Rule 0451 for determination of the API crystal form (*11*).

The size of the API particles in different EZ tablets was determined using a laser confocal micro-Raman imaging system (DXR3xi, Thermo Scientific, USA). The laser confocal micro-Raman spectrometer combines an optical microscope with confocal optical path control to achieve micron-level spatial resolution. It provides high sensitivity and rich spectral information, requires no sample pre-treatment, and operates nondestructively and without contact, thereby enabling the analysis of particle sizes and crystal forms in solid preparations, particularly those with small particle sizes (*12–14*). This method provides an accurate

representation of the API particle size distribution in the EZ tablets following granulation and compression.

Formulation and Microstructural Analysis

The formulation dosages for EZ tablets passing the consistency evaluation tests were not available for two manufacturers and the innovator drug. The laser confocal microscopy micro-Raman imaging system was employed for qualitative and quantitative analyses of the formulations, with a focus on the number of excipients.

The microstructure of the EZ tablets was nondestructively analyzed using laser confocal micro-Raman spectroscopy. Surface preparation involved flat scraping with a razor blade, followed by Raman imaging and subsequent analysis.

Statistical Analyses

This study was conducted in accordance with the guidance issued by the Chinese Center for Drug Evaluation (CDE) of the National Medical Products Administration (*15*, *16*). The model-independent similarity factor method was used to compare the dissolution profiles based on values of f_2 (calculated in Microsoft Excel 2016). If both the generic and innovator drugs dissolve at a rate of 85% or higher within 15 min, then their dissolution profiles can be considered similar (*17*). In such cases, it is not necessary to compare the f_2 values.

RESULTS AND DISCUSSION

Consistency Evaluation

The dissolution profiles of the generic EZ tablets in the four different media are shown in Figure 1, and the f_2 values are presented in Table 2. Four generic EZ tablet brands were subjected to consistency evaluation tests (M1–M4), and these reached dissolution rates of 85% within 15 min in all four media (i.e., exhibiting rapid dissolution) and exhibited consistent intra- and inter-batch uniformity. The remaining manufacturers did not conduct consistency evaluation tests (M5–M12); however, M10 and M11 exhibited rapid dissolution profiles that were comparable to the innovator across all media, and all tablets except M8 achieved rapid dissolution in the HCl (pH 1.2) medium. Tablets sourced from M5–M9 and M12 exhibited poor inter-batch homogeneity and their dissolution profiles differed from that of the innovator drug.

Moisture Content

The moisture content limits of the intermediate granular product particles in the generic EZ tablets exhibited variations (Table 3). The results indicated no correlation between moisture content and dissolution rates.

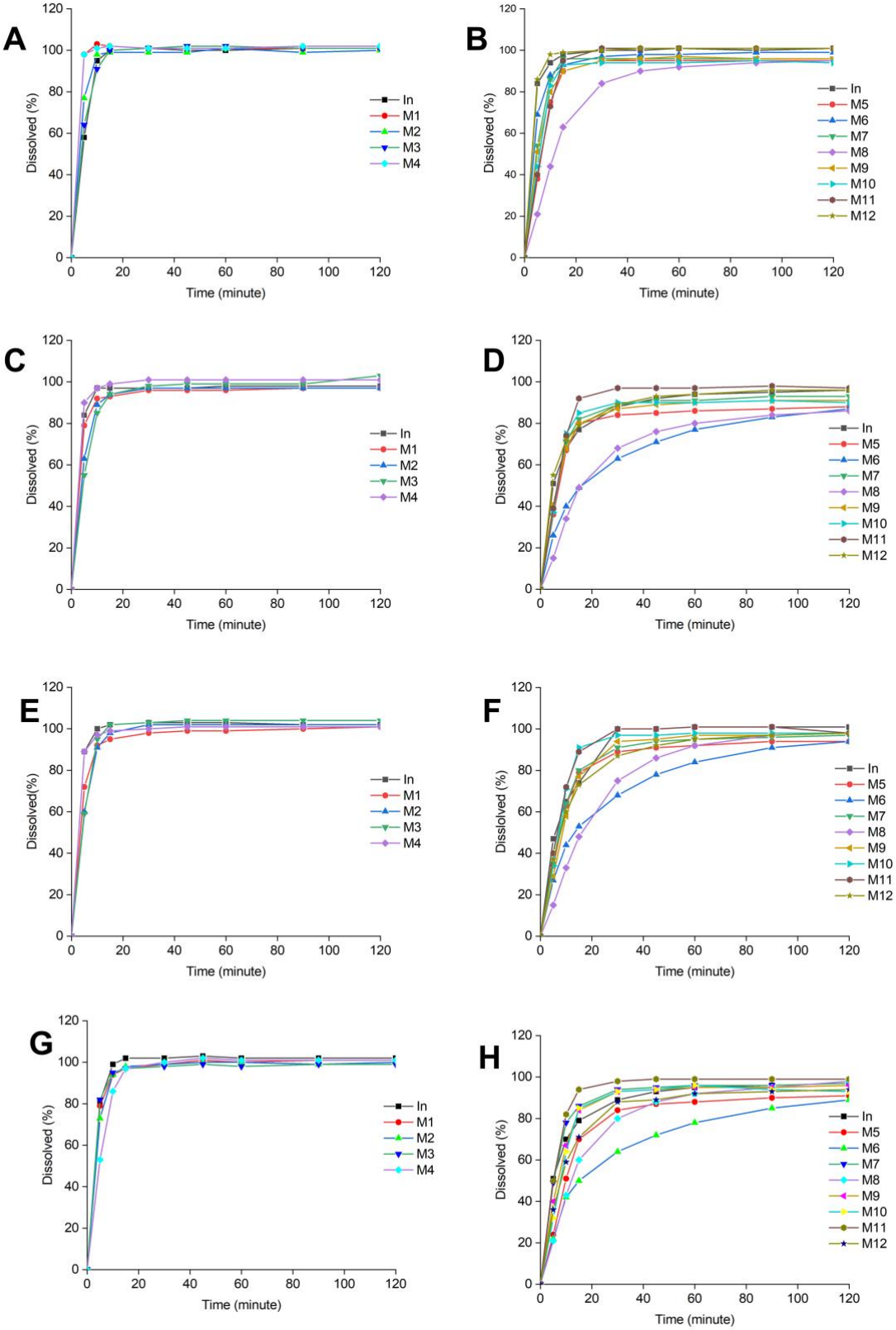

*Figure 1. Dissolution profiles of the innovator (In) drug and generic (M1–M12) estazolam tablets in different media : **A** and **B**: HCl (pH 1.2); **C** and **D**: acetate buffer (pH 4.0); **E** and **F**: phosphate buffer (pH 6.8); **G** and **H**: water. Manufacturers M1–M4 conducted and passed consistency evaluation tests (A, C, E, G), whereas M5–M12 did not conduct consistency evaluation tests (B, D, F, H).*

Table 2. Cumulative Drug Release and f_2 Values for Generic Estazolam Tablets in Four Media (15-Mins)

Consistency Evaluation Status and Manufacturer		Water		HCl (pH 1.2)		Acetate Buffer (pH 4.0)		Phosphate Buffer (pH 6.8)	
		%	f_2	%	f_2	%	f_2	%	f_2
Pass	M1	97	NA	102	NA	93	NA	95	NA
	M2	98	NA	99	NA	94	NA	98	NA
	M3	97	NA	100	NA	94	NA	102	NA
	M4	97	NA	102	NA	99	NA	99	NA
Not Conducted	M5	70	21.1	90	NA	80	27.9	79	22.4
	M6	50	18.7	93	NA	49	21.1	53	19.4
	M7	86	NA	96	NA	82	27.7	80	23
	M8	60	18.5	63	21.3	49	19.8	48	13.9
	M9	84	27.8	90	NA	80	27.9	77	20.3
	M10	85	NA	93	NA	85	NA	91	NA
	M11	94	NA	95	NA	92	NA	89	NA
	M12	71	23.2	99	NA	79	33.5	73	21.9

HCl: hydrochloric acid; NA: not applicable because drug release ≥ 85% within 15 minutes.

API Crystal Form and Particle Size

The XRD patterns from different API manufacturers (i.e., M1, M3, M4, and M13) were essentially uniform (Fig. 2). Therefore, the observed differences in the dissolution profiles are not attributed to variations in the API crystal forms.

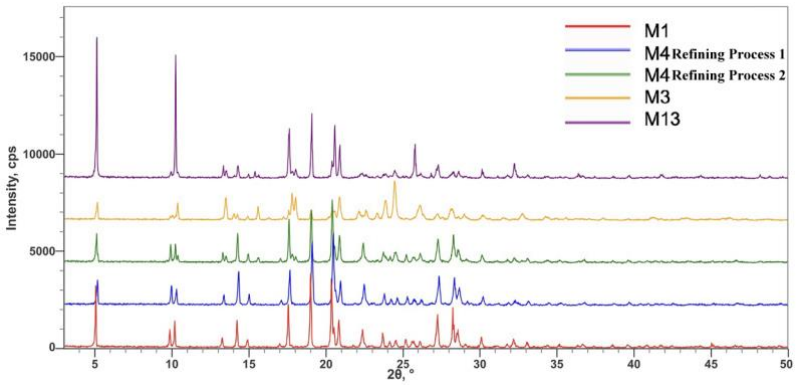

Figure 2. XRD patterns for estazolam tablets sourced from manufacturers of the active pharmaceutical ingredient (M1, M4, M3, M13).

Table 3 presents the API particle size control data for each manufacturer. Tablet brands M1–M4 demonstrated superior control over API particle size, whereas the tablet manufacturers who did not conduct the consistency evaluation tests employed dispersion pretreatment for the API without effective control of particle size. Tablets sourced from M6 and M8 had the largest average API particle sizes, correlating with the lowest dissolution rates (approximately 50%) across all dissolution media after 15 min. This finding emphasizes the importance of controlling API particle size during the development and manufacturing of generic formulations.

Table 3. Comparison of API Particle Size, Moisture Content, and Dissolution Behavior of Intermediate Products from Generic Estazolam Tablets

Consistency Evaluation Status and Manufacturer		API Particle Size and Preparation	Average Particle Size (Raman)	Moisture Content Limit	Moisture Content	Dissolution Behavior
Pass	M1	D50 10–25 μm, D90 ≤ 80 μm	3.744	≤ 3.0%	2.99%	Rapid
	M2	D90 ≤ 15 μm	2.520	1.5–4.5%	3.05%	Rapid
	M3	D90 ≤ 70 μm	3.139	≤ 5.0%	3.08%	Rapid
	M4	D90 ≤ 15 μm	2.728	≤ 3.0%	1.94%	Rapid
Not Conducted	M5	Pass 120 mesh (~125 μm)	3.644	NA	5.04%	Non-rapid
	M6	Not subject to milling process	4.570	3.0–6.0%	5.53%	Non-rapid
	M7	Pass 60 mesh (~250 μm)	3.507	4.0–7.0%	5.85%	Non-rapid
	M8	Pass 120 mesh (~125 μm)	4.051	6.0–9.5%	6.60%	Non-rapid
	M9	Not subject to milling process	2.919	NA	3.78%	Non-rapid
	M10	Pass 100 mesh (~150 μm)	3.074	8–9.5%	8.56%	Rapid
	M11	Crushed (0.6-mm screen)	3.496	1.5–3%	1.79%	Rapid
	M12	Pass 100 mesh (~150 μm)	3.373	NA	5.90%	Non-rapid
Innovator drug	AA1624	NA	3.639	NA	3.22%	Rapid
	AA1625	NA	2.958	NA	3.22%	Rapid

API: active pharmaceutical ingredient; NA: not available (API particle size control limits obtained from the respective manufacturers).

Formulation Analyses

The effects of formulation compositions on the dissolution behavior were analyzed based on data provided by the manufacturers (Fig. 3). Composition of tablets sourced from M1–M4 was similar to that of the innovator drug. The primary excipients included lactose, corn starch, magnesium stearate, and hydroxypropyl cellulose. Lactose was identified as the primary filler and constituted 65% of the formulations. The water solubility of lactose likely facilitates the rapid disintegration of the tablets upon contact with water, thereby enabling particle dispersion without aggregation. These findings suggest a relatively low density of excipients.

Conversely, most tablets that did not undergo consistency evaluation testing exhibited slow dissolution, and their formulations differed significantly from that of the innovator drug, primarily due to variations in filler types, binders, and disintegrant dosages. Some manufacturers incorporated surfactants to enhance dissolution but failed to achieve rapid disintegration. The EZ tablets with formulations similar to that of the innovator drug demonstrated faster disintegration and dissolution. These findings suggest that differences in the composition substantially influence the disintegration behavior and dissolution profile of generic EZ tablet formulations.

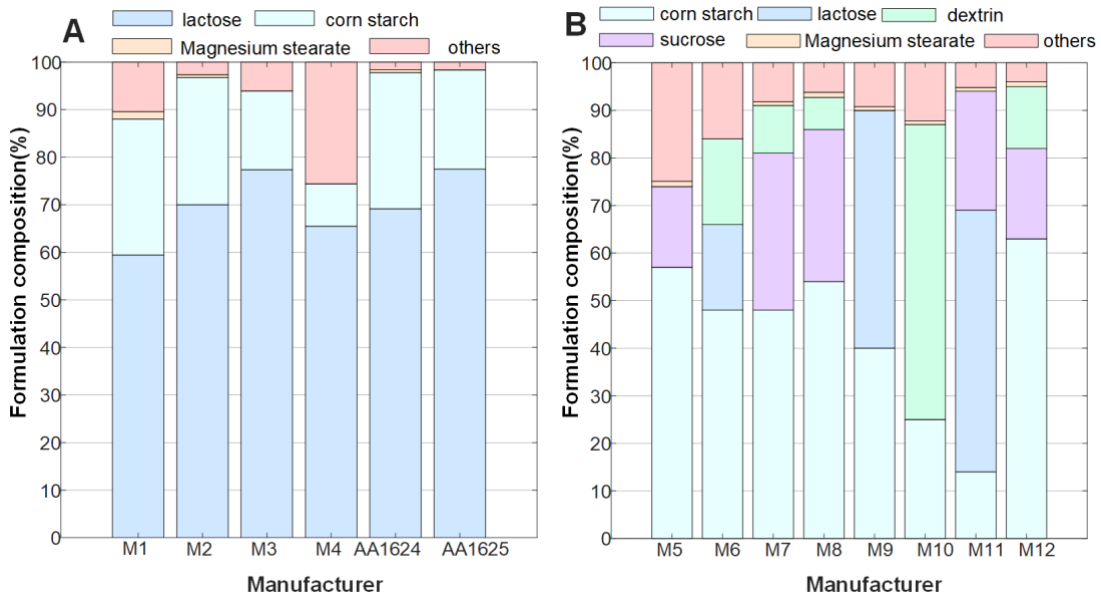

*Figure 3. Composition of estazolam tablet formulations sourced from (**A**) manufacturers who conducted and passed consistency evaluation tests (M1–M4 and the innovator) and (**B**) manufacturers who did not conduct consistency evaluation tests (M5–M12).*

Microstructural Analysis

The microstructural characteristics of tablets sourced from M1–M4 were largely comparable to tablets from the innovator (Fig. 4). These findings are consistent with differences in API particle size control and formulation processes. For M1–M4 tablets, the API was highly dispersed within the excipients, with lactose constituting 65–75% of the formulations, and the microstructural characteristics of these tablets were similar to those of the innovator drug. The M11 tablet contained 50% lactose and exhibited uniform API dispersion, resulting in microstructural and dissolution profiles similar to those of the innovator drug. All other tablets (i.e., those that did not undergo consistency evaluation) exhibited dispersed API agglomerates within the excipients, leading to microstructural variations and poor inter-batch uniformity compared to those of the innovator drug. These findings suggest that the homogeneity of API and excipient dispersion within tablet formulations reflects the variations in formulation processes and influences dissolution profiles.

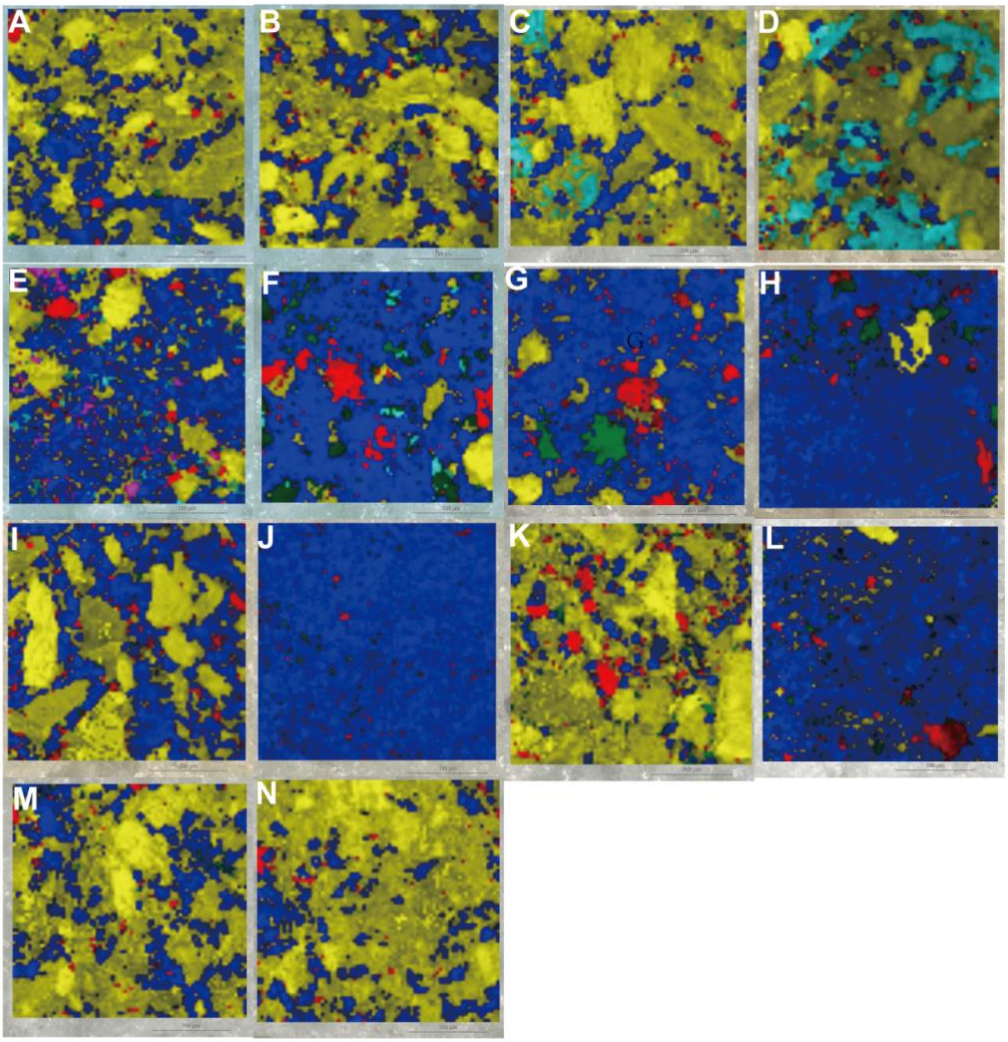

*Figure 4. Microstructural chemical imaging of generic (**A**–**L**) and innovator brand (**M** and **N**) estazolam tablets, as determined by confocal micro-Raman spectroscopy. Scale: 100 µm.*
***A**–**L**: manufacturers 1–12, respectively; **M** and **N**: Innovator AA1624 and AA1625, respectively.*
Red: active pharmaceutical ingredient; blue: starch; green: magnesium stearate; yellow: lactose; purple: sucrose; cyan: microcrystalline cellulose.

Comparative Analyses of Production Processes

A comparative analysis of the manufacturing process data from each manufacturer revealed the consistent use of wet granulation during processing, with variations observed in process parameters across manufacturers. Specifically, variations were observed in the granulation screen aperture, stirring speed, and duration across different manufacturers. Tablets sourced from M1–M4 demonstrated significantly faster disintegration compared to the other tablets. For M1–M4, following tablet disintegration, the API dissolved rapidly from the granules, leaving minimal insoluble excipients at the bottom of the dissolution cup after 15 min. The other tablets exhibited substantial particle retention at the bottom of the cup following disintegration. This observation suggests that the API was ineffectively released from these particles, which adversely affected the API dissolution rate. The findings lead to the hypothesis that variations in production processes influence the rate of API dissolution.

CONCLUSION

This study compared the dissolution profiles of generic EZ tablets from 12 manufacturers in China with that of the innovator drug using four different media (water, HCl, acetate buffer, phosphate buffer). Four tablet manufacturers conducted and passed consistency evaluation tests, demonstrating rapid API release and inter-batch uniformity similar to the innovator. Eight tablet manufactures did not conduct consistency evaluations, and those tablets exhibited slower dissolution profiles, likely due to differences in production processes that may have impaired the therapeutic efficacy. The key factors influencing dissolution were lactose content and uniformity of API dispersion within the excipients, rather than the API crystal form or moisture content. Tablets that did not undergo consistency evaluation exhibited delayed disintegration and particle aggregation, exacerbated by larger API particle size and poor API-excipient dispersion. These findings underscore the importance of consistency evaluations to ensure the quality of generic tablet formulations.

DISCLOSURES

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