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Original Article

Development and Characterization of Sustained Release Solid Dispersions of Chlorzoxazone

Shivakumar Hagalavadi Nanjappa*, Ayesha Samreen, Avichal Kumar, Rushikesh Shinde

Department of Pharmaceutics, KLE College of Pharmacy (A Constituent of KLE Academy of Higher Education and Research, Belagavi), Rajajinagar, Bengaluru, Karnataka, INDIA.

ABSTRACT

Objectives: The research aimed to develop Sustained Release Solid Dispersions (SRSDs) of Chlorzoxazone (COZ) to improve therapeutic efficacy and patient compliance. **Materials and Methods:** SRSDs were developed by the bottom-up solvent evaporation technique with various polymers, comprising Eudragit RL100, ethyl cellulose, Eudragit RS100, and cellulose acetate. **Results:** All eight SRSDs batches exhibited good flow properties with the Carr's index, angle of repose, and Hausner's ratio ranging from 11.56±0.01 to 14.89±0.02, 22.03±0.02º to 25.24±0.03º, and 1.11±0.05 to 1.24±0.03, respectively, indicating suitability for further processing. Drug loading and percentage yield were found to range between 72.28±2.36 to 88.25±2.78% and from 65.23±2.23 to 90.41±2.97% respectively. SEM and optical microscopy revealed the reduction in size of the SRSDs, while Fourier transform infrared spectroscopy proved the drug integrity in the formulations. X-ray diffraction and Differential Scanning Calorimetry confirmed a drop-in drug crystallinity in the SRSDs. The *in vitro* drug release studies of SRSDs were found to range from 62.32±5.4% to 94.93±9.81% in 8 hr. Batch F5 emerged as the best formulation, displaying the most desirable drug release profile with minimal burst effect (29.97±2.75% in 1 hr) and 78.11±6.18% at 8 hr. The drug release from F5 appeared to follow first-order kinetics governed by Higuchi diffusion and Fickian transport mechanisms. **Conclusion:** The studies proved that the bottom-up solvent evaporation method was employed to successfully produce SRSDs of COZ, which prove to be an ideal platform that can ensure a prolonged, yet complete release of the drug.

Keywords: Chlorzoxazone, Bioavailability, Sustained release solid dispersions, Solvent evaporation.

Correspondence:
Dr. Shivakumar Hagalavadi Nanjappa
Professor, Department of Pharmaceutics, KLE College of Pharmacy, Rajajinagar, Bengaluru-560010, Karnataka, INDIA.
Email: shivakumarhn@gmail.com

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INTRODUCTION

Several formulations have been investigated and developed over the previous few decades to prevail over the issue of solubility, including strategies like forming salts, utilizing self-emulsifying delivery systems, incorporating cosolvents, designing cocrystals, complexing with cyclodextrins, developing Amorphous Solid Dispersions (ASDs), and employing nanoparticle formulations.[1] Amongst all the above, ASDs have been extensively investigated to enhance the drug's apparent solubility beyond its equilibrium solubility in the crystalline form.[2] ASDs are regarded as more beneficial than the alternative approaches because they increase solubility without affecting the permeability.[3] Recent studies confirm that ASDs can maintain supersaturation longer than cyclodextrins or cosolvents, making them particularly valuable for enhancing oral bioavailability.[4] Compared to nanocrystals or lipid-based systems, ASDs also offer better manufacturing scalability and stability.[5]

ASDs are formulated by different approaches, like hot melt extrusion, spray drying, and solvent evaporation, considered the most common approach.[6] This approach is successfully exploited to impart sustained release properties for the drugs that are poorly water-soluble and possess a shorter biological half-life.[7] The release rate from these ASDs can be optimized by reducing the tendency of recrystallization by decreasing the rate of supersaturation using certain sustained-release polymers.[8] Solid dispersions developed using these polymers can impart sustained release properties and minimize the dosing frequency.[9] Sustained Release Solid Dispersions (SRSDs), in contrast to conventional tablets, if appropriately developed, can display sustained release properties and, at the same time, ensure the complete release of therapeutic agents that exhibit solubility issues.[10] Therefore, SRSDs would add value to BCS (Biopharmaceutical Classification Scheme) class II molecules that normally display poor solubility and therefore tend to exhibit an incomplete release of the therapeutic agent from dosage forms.[11] The drug release from SRSDs can be regulated, as the API is generally presented in a relatively amorphous form within the sustained-release polymer

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matrix, allowing for controlled and prolonged release.[12,13] Moreover, these SRSDs are known to exhibit more reproducible gastric and intestinal emptying times compared to the single-unit counterparts.

Skeletal Muscle Relaxants (SMRs) have been administered to treat several musculoskeletal conditions. SMRs such as cyclobenzaprine, chlorzoxazone, carisoprodol, methocarbamol, tizanidine, and baclofen are known to be centrally acting and, in some cases, on spinal motor neurons.[14] Chlorzoxazone (COZ) is a commonly used centrally acting musculoskeletal relaxant that continues to be the first line of therapy in the management of muscle spasms. The mechanism of action of COZ primarily involves its activity in the subcortical regions of the brain and the spinal cord, where it exerts its muscle relaxant effects by depressing polysynaptic reflex pathways.[15] However, the drug needs to be administered 3 to 4 times a day due to its short half-life (1 to 2 hr), making it a suitable candidate to develop a sustained-release dosage form. The drug is listed under the BCS Class II, as it displays lower solubility in the aqueous phase, and therefore exhibits a dissolution rate limited by absorption.[11]

The primary objective of the current work is to design SRSDs of COZ, which would ensure prolonged yet complete drug release to reduce the dosing frequency. Characterization of the solid state of COZ in the polymer matrix would constitute an integral part of the work, in addition to the evaluation of *in vitro* drug release from SRSDs. The present investigation was novel and the first-of-its-kind, as no such study pertaining to the development of SRSDs has been reported for COZ.

MATERIALS AND METHODS

Materials

Chlorzoxazone (COZ) was graciously provided by Aarti Industries Ltd., Mumbai. Eudragit RS 100 (15mPa.s) and Eudragit RL 100 were generous gift samples donated by Degussa (I) Ltd., Ethyl cellulose (5% solution, 18-20mPa.s), cellulose acetate (22 to 38mPa.s), and other chemicals were purchased from SD Fine Chemicals, Mumbai.

Methods

Preparation of Sustained Release Solid Dispersions of Chlorzoxazone

Eight batches of SRSDs of COZ were prepared using the bottom-up solvent evaporation method, as depicted in Figure 1, employing sustained release polymers.[16] COZ and polymers were weighed in pre-determined ratios and dissolved completely in the organic solvent. Cellulose acetate was dissolved in acetone, while Eudragit RS100, Eudragit RL100, and ethyl cellulose were individually dissolved in ethanol to prepare clear 5% w/w polymer solutions. Initially, the polymers were dispersed in the respective solvents to form a uniform dispersion using a high shear homogenizer (T18, Ultra Turrax®, IKA®, Bengaluru) at 10000 rpm for 10 min at room temperature to obtain a homogeneous, clear solution. COZ was incorporated into the polymeric solution and further homogenized to obtain a clear solution. After the COZ and polymer were fully dissolved in the solvent, the mixture was subjected to drying under reduced pressure (100 mmHg) using a rotary evaporator (Serwell Instruments Inc., Bengaluru) to obtain SRSDs.[17] The resulting SRSDs were ground and sieved through a #44 mesh (355 µm). The drug-to-polymer ratio of the drug was varied to produce eight different batches of SRSDs as indicated in Table 1.

Evaluation of Chlorzoxazone Sustained-Release Solid Dispersion

Micromeritics Properties of SRSDs

The micromeritic characteristics of COZ-SRSDs, including bulk density (D_{Bulk}), angle of repose (θ), tapped density (D_{Tapped}), Hausner Ratio (HR), and Compressibility Index (CI), were determined. Tapped density was measured by transferring 20 g of the sample into a 50 mL graduated cylinder and subjecting it to 50 taps per min. using a tap density tester (Campbell Electronics, Mumbai, India) until a constant volume was achieved. The D_{Bulk} was calculated by filling a known amount of sample into the same cylinder and tapping it thrice. The Tapped Volume (TV) and Bulk Volume (BV) are utilized to calculate densities. The values of D_{Bulk}

Table 1: Composition of prepared sustained-release solid dispersions of Chlorzoxazone.

Formulations	Chlorzoxazone (mg)	Ethyl cellulose (mg)	Cellulose acetate (mg)	Eudragit RL100 (mg)	Eudragit RS100 (mg)
F1	100	100	-	-	-
F2	100	-	100	-	-
F3	100	-	-	100	-
F4	100	-	-	-	100
F5	100	-	-	-	50
F6	100	-	50	-	-
F7	100	-	-	-	25
F8	100	-	25	-	-

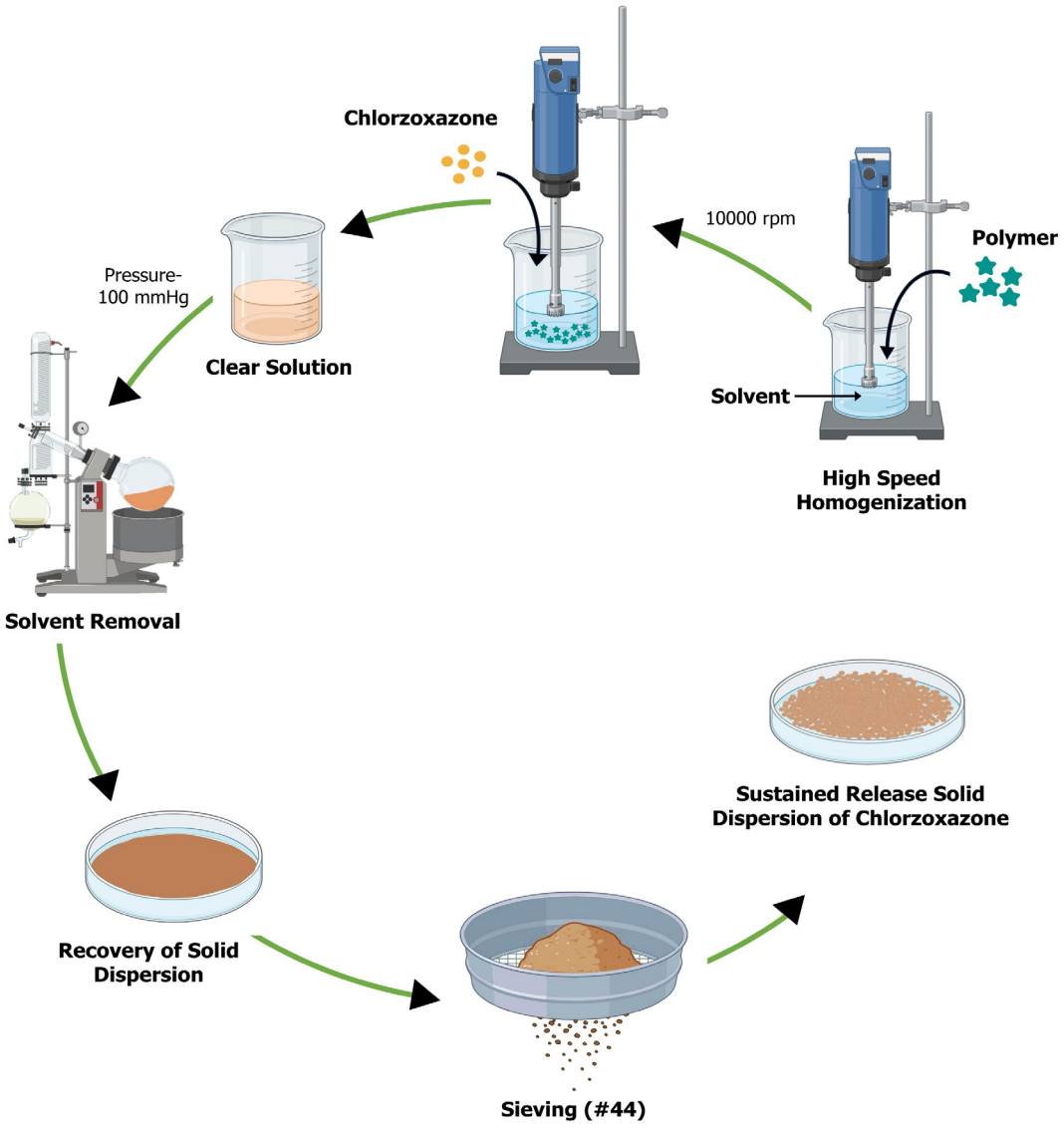

Figure 1: Illustration method of preparation of Chlorzoxazone sustained-release solid dispersion.

and D_{Tapped} were then used to derive the Hausner Ratio (HR) and Carr's index (CI) using the equations (Eq. 1 to Eq. 4).[18,19]

$$Tapped Density\ (g/mL) = \frac{Mass(g)}{TV\ (mL)} \text{----------(1)}$$

$$Bulk Density\ (g/mL) = \frac{Mass(g)}{BV\ (mL)} \text{----------(2)}$$

$$Hausner's Ratio\ (HR) = \frac{D_{Tapped}}{D_{Bulk}} \text{----------(3)}$$

$$Compressibility\ Index(\%) = \frac{D_{Tapped} - D_{Bulk}}{BV\ (mL)} \times 100 \text{-------(4)}$$

Using the fixed funnel method, the powder sample was allowed to pass through a funnel placed 2.5 cm above a horizontal surface. Once the cone formed reached the funnel's tip, its height and diameter were measured to determine the angle of repose (Eq. 5).[20]

$$\text{Angle of Repose } (\theta) = tan^{-1}\frac{H}{R} \text{----------(5)}$$

where 'H' is the height and 'R' is the radius of COZ-SRSD's pile

Fourier Transform Infrared Spectroscopy (FTIR)

IR spectra of COZ and SRSDs were taken using an FTIR spectrophotometer (Jasco 450, Eaton, MD, USA) (in the range of 4000-400 cm^{-1}) to identify any structural changes resulting from the formulation process. Potassium Bromide (KBr) was used to dilute the samples, which were then analyzed using a diffuse reflectance sampler prior to exposure to IR rays.[21]

Determination of SRSDs Yield

The yield refers to the total quantity of SRSDs obtained after the formulation process. The percentage yield of SRSD of COZ was calculated based on the initial weight of COZ and the polymer used to produce the batch of SRSDs.[22] The practical batch yield was calculated based on the final dried weight of the SRSDs. The

theoretical yield was estimated by combining the starting weights of COZ and the respective polymer used in the formulation. The yield (%) was calculated using Eq. 6.

$$Yield(\%) = \frac{PracticalYield}{TheoreticalYield} \times 100 \text{----------(6)}$$

Optical Microscopy

A small amount of SRSDs were mounted on a clean glass slide and overlaid with a coverslip. COZ-SRSDs were observed using optical microscopy (LABOMED, Vision-2000, India) with suitable magnification. Subsequently, a stage micrometer that has a precisely etched scale (typically 10 µm per division) was observed under the microscope. An eyepiece micrometer, a glass disc with an arbitrary scale inserted into the eyepiece of the microscope, was calibrated using a stage micrometer.[23,24]

Scanning Electron Microscopy (SEM)

The SRSDs were affixed onto specimen holders with double-sided conductive carbon tape. To improve conductivity and minimize charging during imaging, a thin gold layer (around 200 nm) was sputter-coated onto the samples under a vacuum of sputter-coated (JFC-1100E, JEOL Ltd., Tokyo, Japan) for 5 min. under a pressure of 0.001 Torr. The gold-coated samples were subsequently examined under a scanning electron microscope (JSM-840A, JEOL Ltd., Tokyo, Japan). Photomicrographs were captured at appropriate magnifications to analyse the surface characteristics and particle characteristics of the SRSD formulations.[25]

Drug Loading

SRSDs (10 mg equivalent) were weighed and transferred to a 10 mL volumetric flask containing Phosphate Buffer Solution (PBS), pH 6.8. The dispersion was sonicated using an ultra-sonicator (GT sonic, Meizhou, China) for 10 min to separate undissolved excipients. The dispersions were then filtered and appropriately diluted with PBS (pH 6.8) before checking the absorbance of the solution at 280.4 nm using a UV Spectrophotometer (Model UV 1900i, Shimadzu Corporation, Tokyo, Japan), using PBS (pH 6.8) as a blank.[26] The percentage drug loading was determined using Eq. 7. The data were generated in triplicate, and the results were expressed as the mean and the standard deviation.

$$\text{Drug Loading (\%)} = \frac{Weight\ of\ Chlorzoxazone\ in\ Solid\ Dispersion}{Weight\ of\ theoritical\ Chlorzoxazone\ amount} \times 100 \text{----------(7)}$$

Differential Scanning Calorimetry (DSC)

An accurately weighed amount of each sample (typically 3-8 mg) was loaded into an aluminum sample pan for analysis and sealed hermetically to prevent moisture loss or sample degradation. This SRSDs analysis was carried out using Differential Scanning Calorimeter (Model Pyris-1, PerkinElmer, LLC, Norwalk, CT, USA). Samples were heated from 20°C to 220°C at a constant rate of 10°C per min. in an environment of nitrogen at a flow rate of 30 mL/min.

Crystallinity Assessment by X-ray Diffraction (XRD)

An X-ray Diffractometer (Model PW 1050/37, Philips, Almelo, Netherlands) was utilized to compare the crystalline characteristics of SRSDs with COZ. Diffractograms of COZ, a physical mixture of drug and polymers, and SRSDs were recorded using monochromatic CuK α radiation filtered through nickel, operated at 40 kV.[27] A current (20 mA) at a glancing angle, X-ray diffraction was employed at a scan rate of 40°/min in a 2θ range of 0° to60°. The Degree of Crystallinity (DC) can be quantified with the help of Eq.8.

$$\text{DC (\%)} = \frac{PH_{sample}}{PH_{refer}} \times 100 \text{ ----------(8)}$$

Where the 'PH_{sample}' indicates the height of the most intense peak in the sample spectrum, and 'PH_{refer}' represents the peak height of the reference (pure COZ) at the corresponding 2θ angle.

In vitro drug release profile

Dissolution profile evaluation is essential to evaluate the performance and release behavior of COZ-SRSDs. These experiments mimic gastrointestinal conditions to evaluate the drug release profile from the formulation over time. A USP Type I dissolution apparatus (Model TDT-08T, Electro-lab Ltd., Mumbai) was employed to study the release behavior of COZ-SRSDs. A two-phase dissolution medium, namely 0.1 N hydrochloric acid (900 mL) for the first 2 hr, followed by PBS (pH 6.8) for the next 6h, was used for the study. The dissolution medium was maintained at a temperature of 37±0.5°C and agitated at a constant speed of 100 rpm. At predetermined 1-hr intervals, aliquots (5 mL) were taken out and immediately replenished to maintain sink conditions. The absorbance of the collected samples was recorded at 280.4 nm using a UV-visible spectrophotometer, and the cumulative percentage of drug released was plotted as a function of time.[28,29] The data was recorded in triplicate, and the results were expressed as the mean and the standard deviation.

Kinetic Models with Release Mechanism

Attempts were made to fit the dissolution data of the SRSDs into a first-order model (Eq. 9) to determine the drug release kinetics. This analysis aids in evaluating the drug release kinetics and comparing the release behavior among various formulation batches.

$$Q_t = Q_0 e^{-k_1 t} \text{----------(9)}$$

Where Q_0 and Q_t indicate the drug release levels at specific time intervals, 0 and at a time 't', respectively, 'K_1' is the first-order rate constant.[30]

The dissolution data were analyzed by fitting into various mathematical models, including the Higuchi diffusion model (Eq. 10) and the Korsmeyer-Peppas model (Eq. 11), to understand and characterize the underlying mechanism of drug release.[31]

$$Q_t = K_H\sqrt{t} \text{ ----------(10)}$$

$$\frac{Q_t}{Q_\infty} = K_p t^n \text{ ----------(11)}$$

Where, 'Q_t' is drug release amount at time 't', 'K_H' is the Higuchi release constant reflecting the rate of diffusion, 'Q_∞' is the maximum amount of drug released achievable over an infinite period, 'K_p' is the formulation-dependent release rate constant, and 'n' is the release exponent used to characterize the underlying drug release mechanism.

RESULTS

The SRSDs of COZ were prepared using the solvent evaporation method, utilizing various drug-to-polymer ratios based on preliminary studies. Eight batches of SRSD formulations (F1-F8) of COZ were developed using various polymers such as Eudragit RS 100, cellulose acetate, Eudragit RL 100, and ethyl cellulose by the drug-to-polymer ratio. The drug-to-polymer ratio of formulations F1 to F4 was 1:1, while formulations F5 and F6 had a ratio of 2:1, and F7 and F8 had a ratio of 4:1. Efforts were made to identify the right solvent system for the blend of the drug and polymer. Ethanol was used as a solvent to dissolve the drug and ethyl cellulose, as well as Eudragit. In the case of cellulose acetate, acetone was employed as a solvent. The high-speed homogenization ensures that both the drug and the polymers are molecularly dispersed to form a clear solution before drying following solvent removal. The process can impart sustained release properties to the SRSDs of COZ based on the nature of the polymer. The clear solutions obtained were finally dried under reduced pressure in a flash evaporator to hasten the drying process. Then the dried SRSDs were used for further evaluations.

Micrometric properties

The micromeritics properties for the COZ-SRSDs indicated flowability and compressibility. The angle of repose for the SRSD ranged from 22.03±0.02º to 25.24±0.03º. Further, the Carr's index was found to range from 11.56±0.01 to 14.89±0.02, while the Hausner ratio varied between 1.11±0.05 to 1.24±0.03 (Table 2). These results indicate that all COZ-SRSDs (F1-F8) exhibited satisfactory micromeritic properties, reflecting good flow behaviour and compressibility.

Fourier Transform Infrared (FTIR)Spectroscopy

COZ revealed the characteristic peaks that can be assigned corresponding to the observed peaks correspond to alkane (C-H) stretching, alkene (=C-H) and amine (N-H) stretching, C-N and C-Cl bond stretching, as well as C=O stretching vibrations attributed to the carboxylate functional group. These peaks are indicative of the intact functional groups in the drug molecule. The characteristic peaks of the different functional groups of COZ-SRSDs are captured in Table 3.

Percentage Yield

The percentage yield of the eight batches of COZ-SRSDs ranged from 65.23±2.23% to 90.41±2.97% which depended mainly on the proportion of polymer used, depicted in Figure 2A. The first four batches, F1 to F4, that were produced with to drug-to-polymer ratio of 1:1, displayed a significantly higher yield compared to those produced with a ratio of 2:1 (F5 and F6) and 4:1 (F7 and F8).

Optical Microscopy

Optical microscopy revealed substantial variations in Particle Size (PS) across different batches of SRSDs as the proportion of polymer changed. The PS of SRSDs was found in the range of 21.65±3.22 µg and 99.92±3.56 µg. The PS data of SRSDs obtained by optical microscopy are represented in Figure 2C.

Scanning Electron Microscopy (SEM)

SEM was employed to analyze the surface morphology of the SRSD formulation. The SEM images revealed that the COZ displayed needle-shaped crystals observed at a 3 µm scale, with a size range between 1.970 to 5.479 µm, displayed in Figure 3A. On the contrary, the photomicrographs of SRSD (F5) indicated smaller particles at 1µm, as indicated in Figure 3B.

Table 2: Micromeritics properties of COZ-SRSDs.

Formulations	CI (%)	HR	AOR (º)
F1	11.56±0.01	1.11±0.05	22.03±0.02
F2	12.02±0.02	1.17±0.01	22.27±0.03
F3	12.05±0.02	1.18±0.04	22.53±0.07
F4	12.36±0.03	1.19±0.02	22.98±0.05
F5	13.54±0.06	1.18±0.06	23.51±0.06
F6	13.25±0.06	1.24±0.03	23.38±0.04
F7	14.89±0.02	1.19±0.08	25.24±0.03
F8	14.82±0.01	1.20±0.03	24.12±0.03

*All data represent as Mean±SD (n=3). CI: Carr's Index, HR: Hausner's Ratio, AOR: Angle of Repose.

Table 3: Fourier Transform Infrared (FTIR) Spectroscopical Data.

Functional Group	Literature value	Characteristic peaks of Chlorzoxazone	Characteristic peaks of SRSD
C-H	3100 - 3000 cm^{-1}	3058.55 cm^{-1}	---
C-C	1600 - 1585 cm^{-1}	1621.84 cm^{-1}	1621.84 cm^{-1}
C-H	1000 - 650 cm^{-1}	804.171 cm^{-1}	803.206 cm^{-1}
N-H	3400 - 3250 cm^{-1}	3471.24 cm^{-1}	3472.2 cm^{-1}
C-N	1335 - 1250 cm^{-1}	1260.45 cm^{-1}	1260.25 cm^{-1}
C-Cl	800 - 550 cm^{-1}	733.782 cm^{-1}	733.782 cm^{-1}
C=O	1780 - 1665 cm^{-1}	1694.16 cm^{-1}	---

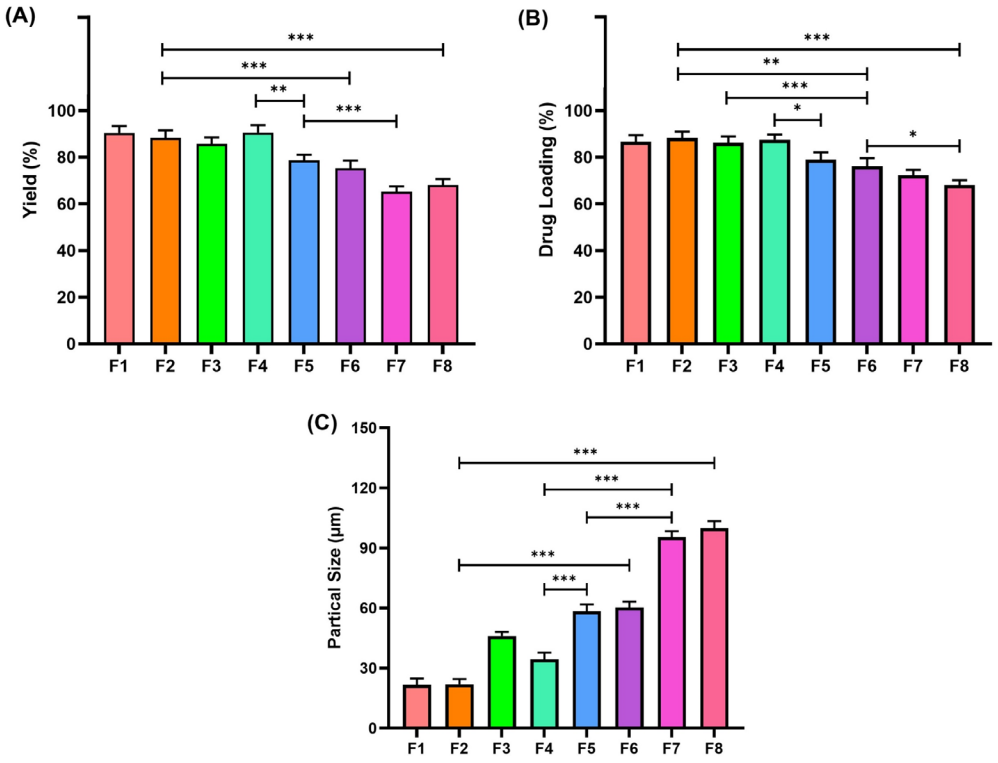

Figure 2: Evaluation of yield (A), drug loading (B), and particle size (C) of Chlorzoxazone Sustained Release Solid Dispersion (SRSD) formulations. Data are presented as mean±S.D. (n=3). Statistical significance levels: *p<0.05, **p<0.01, and ***p<0.001.

Drug Loading

The drug loading for the COZ-SRSD formulation ranged from 72.28±2.36 to 88.25±2.78%. As increase in polymer concentration drug loading also increases, as displayed in Figure 2B. Batch F5 shows 78.99±3.15% of drug loading with the help of Eudragit RS 100 with a median concentration.

Differential Scanning Calorimetry (DSC)

The DSC thermogram of pure COZ, as shown in Figure 4A, displayed a well-defined endothermic transition at 192.79 °C, indicating the melting point of the COZ and confirming its well-defined crystal framework. In contrast, Figure 4B, which represents Physical Mixture (PM) thermograms of COZ with polymers, displays a broad endothermic band at 178.97°C. As shown in Figure 4C, the thermogram of SRSD (formulation F5) exhibits a broad endothermic band. The original melting peak of COZ is completely absent.

X-ray Diffraction (XRD)

The XRD analysis revealed distinct crystallinity patterns across the samples. As shown in Figure 5A, the COZ exhibited sharp and intense peaks at 2θ values of 10.6°, 11.5°, 12.1°,12.8°, 13.2°,

13.8°, 15.5°, 16.3°, 17.8°, 19.9°, 21.1°, 21.6°,25.2°, 25.8°, 27.5°, 28.1°, 29.4°, 30.3°, and nearly 38.3°. The physical blend of the drug and polymer exhibited both crystalline and amorphous characteristics, as shown in Figure 5B, with prominent drug peaks at 2θ values of 10.6°, 18.8°, 20.3°, and 28.4°. SRSDs exhibited significantly diminished and broadened peaks as shown in Figure 5C, with few characteristic crystalline peaks still detectable at 2θ values of 27.5°, 24.6°, and 20.4° but at much lower intensity and resolution.[31]

A notable reduction in the characteristic intensities in the COZ XRD peak was observed in both the physical mixture with 2034 counts per second (cps) and the final formulation (1980 cps), compared to the pure drug, which exhibited a peak intensity of 3250 cps at approximately 2θ values of 19°. Furthermore, the number of peaks exceeding 1500 cps decreased from seven in COZ to four in the physical mixture and further to three in the formulated product.

In vitro release study

The *in vitro drug* release behaviour of COZ-SRSDs was evaluated in a buffer of pH 1.2 for 2 hr, followed by a buffer of pH 6.8 phosphate buffer for 6 hr. Drug release varied from 62.32±5.4% to 94.93±9.81% depending on the type and proportion of polymers (Figure 6). The outcomes of the curve fitment data are captured in Table 4.

DISCUSSION

Eudragit RS 100 and RL 100 are ammonia-methacrylate copolymers widely used in sustained-release formulations.[32] RS 100 exhibits low permeability, making it suitable for prolonged drug release, while RL 100 has higher permeability, allowing for adjustable drug release rates when blended with other polymers.[33] These polymers are insoluble across the pH range, ensuring consistent drug release in gastrointestinal conditions.[34] Ethyl cellulose is a hydrophobic polymer commonly employed in controlled-release coatings and matrices due to its water-insoluble nature and robust film-forming properties. It is particularly useful in modulating drug diffusion and preventing premature drug release.[35,11] Cellulose acetate, a semi-permeable polymer, is frequently used in osmotic drug delivery systems and pH-independent coatings. Its solubility in organic solvents allows for flexible formulation design, while its ability to form

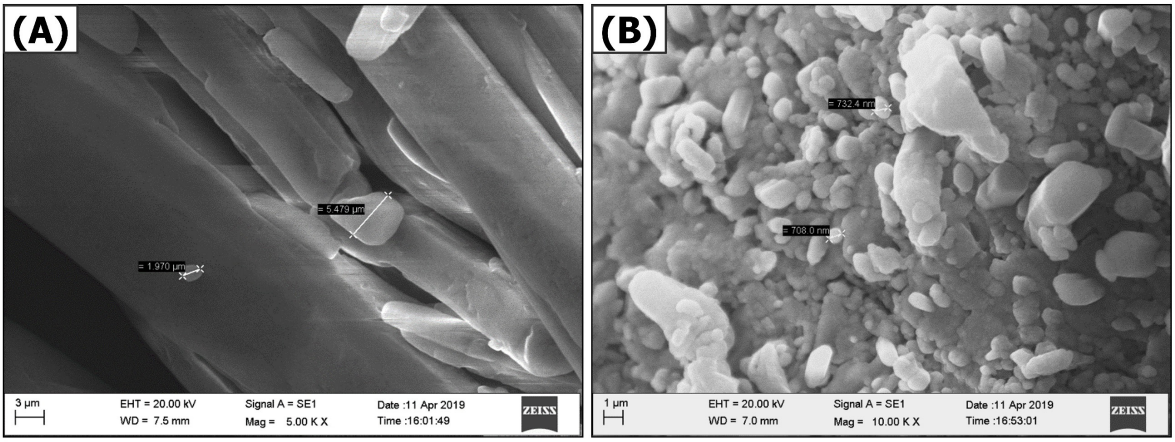

Figure 3: Scanning electron micrographs of pure Chlorzoxazone (A) and SRSD formulation F5 (B).

Table 4: Curve Fitting Results of *in vitro* Dissolution Data for the Sustained Release Solid Dispersion Formulation using various Kinetic Models.

Batch	Higuchi Plot		Korsmeyer-Peppas Plot			First Order Plot	
	* K_H (%.$h^{-1/2}$)	R^2	'n' Value	* K_p (h^{-n})	R^2	* K_1 (h^{-1})	R^2
F1	24.01±0.59	0.978±0.02	0.3572±0.02	0.32±0.01	0.970±0.01	0.17±0.03	0.945±0.002
F2	24.06±0.12	0.969±0.04	0.3659±0.03	0.32±0.00	0.964±0.02	0.17±0.14	0.917±0.010
F3	22.03±0.42	0.982±0.00	0.4936±0.02	0.22±0.01	0.961±0.01	0.16±0.25	0.933±0.012
F4	23.89±0.30	0.987±0.06	0.5089±0.05	0.23±0.02	0.962±0.01	0.17±0.07	0.962±0.043
F5	27.62±0.18	0.981±0.04	0.4344±0.08	0.57±0.01	0.967±0.03	0.19±0.21	0.960±0.040
F6	26.57±0.06	0.874±0.04	0.2064±0.01	0.49±0.03	0.978±0.02	0.18±0.45	0.803±0.005
F7	28.14±0.17	0.809±0.03	0.1523±0.08	0.35±0.02	0.933±0.02	0.19±0.46	0.727±0.015
F8	33.56±0.20	0.744±0.02	0.1005±0.02	0.77±0.02	0.979±0.04	0.35±0.04	0.805±0.018

*All data represent as Mean±SD (n=3).

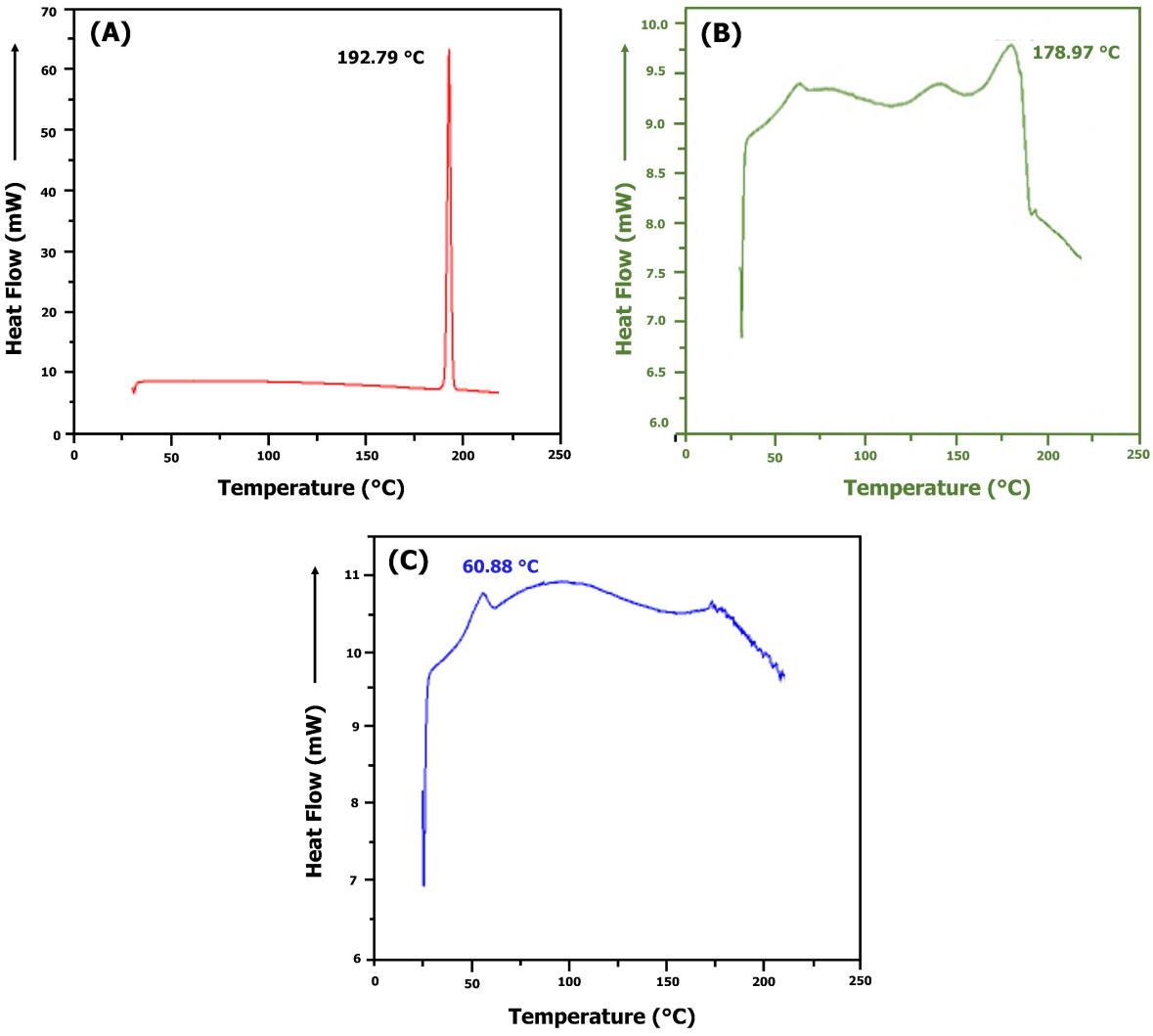

Figure 4: DSC thermographs of pure Chlorzoxazone (A), physical mixture of Chlorzoxazone and polymers (B), and sustained release solid dispersion formulation F5 (C).

stable films ensures controlled drug release.[12,13] These polymers play a critical role in pharmaceutical formulations by enabling precise control over drug release kinetics based on their unique physicochemical properties.[36]

The micromeritic evaluation of the COZ-SRSD formulations (F1-F8) demonstrated favorable flow and compressibility characteristics. The angle of repose, Carr's Index, and Hausner's ratio correspond to good to fair flow behavior and acceptable compressibility. Collectively, these results indicate that the COZ-SRSD powder blends possessed satisfactory micromeritic qualities suitable for downstream processing such as tablet compression or capsule filling.[37] The flowability of the COZ-SRSDs followed the order: Ethyl cellulose >Cellulose acetate >Eudragit RL100 >Eudragit RS100. Among these, ethyl cellulose exhibited the best flow characteristics, likely due to its larger PS and lower cohesive nature compared to the other polymers used.

Calibration for FTIR was routinely performed using standard polystyrene films to verify wavenumber accuracy and instrument performance, following pharmacopeial protocols. Samples were prepared by thoroughly grinding the drug-polymer mixture with dry KBr powder (used in a ratio of 1:100) before loading into a diffuse reflectance sampler to ensure uniform optical pathlength and reproducibility. Drug-excipient compatibility studies are crucial to confirm any possible chemical interactions between the API and formulation excipients.[38] FTIR is a widely used analytical technique for identifying possible interactions by analyzing characteristic functional group vibrations at the molecular level. The FTIR spectra clearly exhibited all characteristic peaks corresponding to functional groups of COZ, such as alkane (C-H), alkene (=C-H), amine (N-H), C-N, C-Cl, and the carboxylate (C=O) vibrations, without any shifts or disappearance of bands upon formulation with the polymer matrix. FTIR analysis confirmed the absence of significant drug-polymer interactions, as all characteristic peaks remained unchanged in the SRSDs. The results obtained correspond well with the characteristic peaks of COZ that have been reported earlier.[39] The presence of characteristic COZ peaks in the spectra of SRSDs indicates that

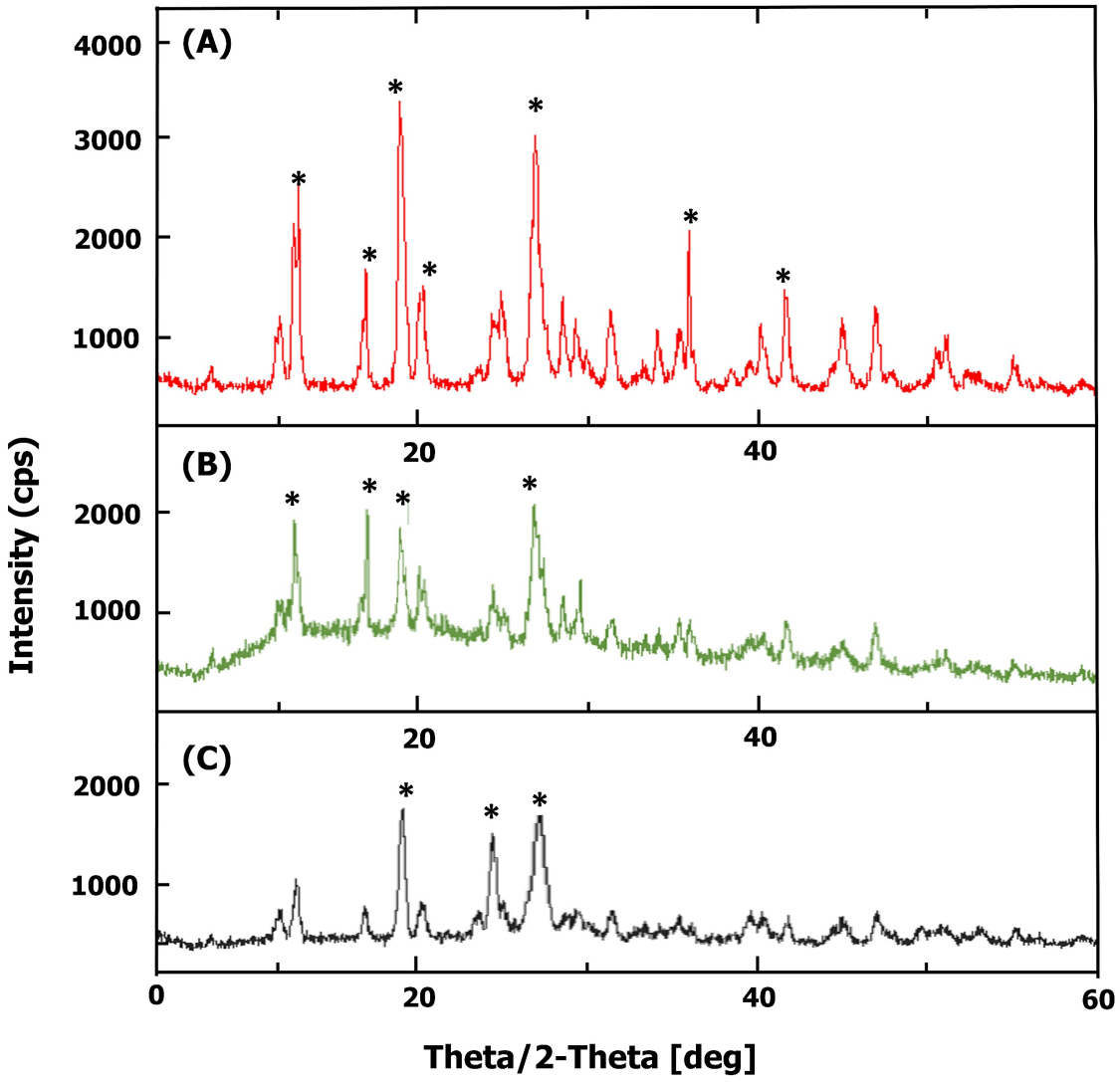

Figure 5: X-ray Diffraction graphs of Pure Chlorzoxazone (A), Chlorzoxazone with polymers physical mixture (B), and Chlorzoxazone Sustained Release Solid Dispersion-Formulation F5 (C), *CPS: Counts per second.

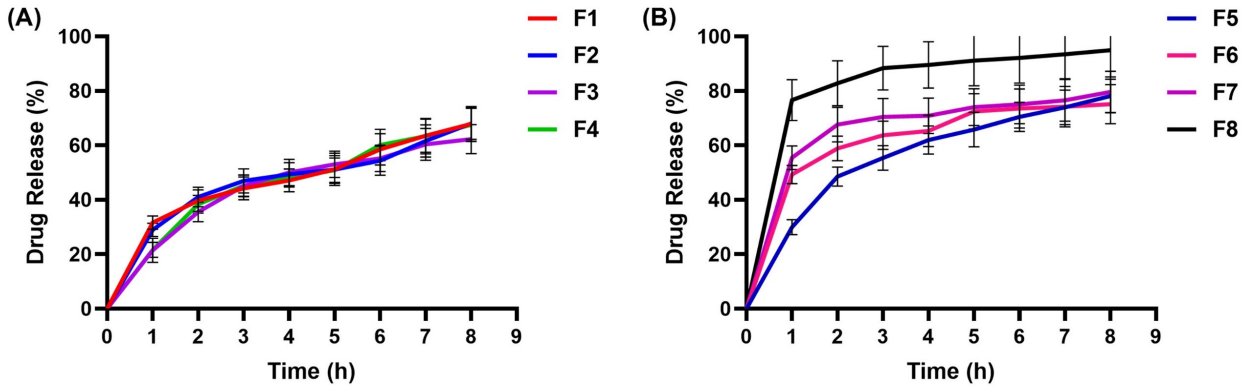

Figure 6: *In vitro* Drug Release Profiles of Chlorzoxazone Sustained-Release Solid Dispersions: Formulations F1-F4 (A) and Formulations F5-F8 (B). Data are presented as mean±S.D. (*n*=3).

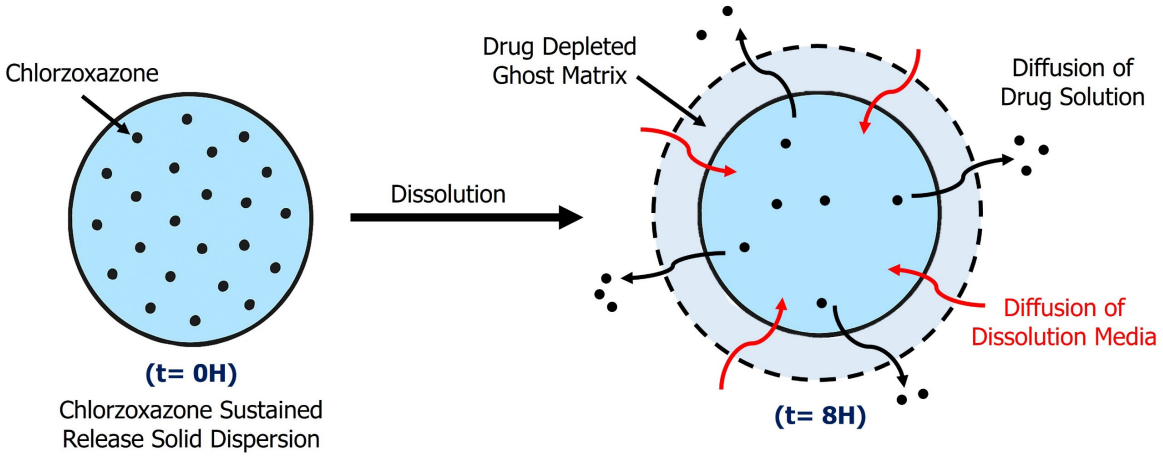

Figure 7: Schematic Illustration of Drug Release and Ghost Matrix Formation in Chlorzoxazone Sustained-Release Solid Dispersion During Dissolution.

no major interactions occurred between the active ingredient and excipients throughout formulation development. Thus, the characteristic spectral peak of COZ present in the SRSDs confirmed that the drug's structural integrity was preserved within the formulation. The results confirmed that no chemical incompatibility existed between COZ and the excipients utilized in the preparation of the SRSDs. Additionally, the consistency of IR peaks noted in COZ and formulation ruled out the chances of degradation or interaction.

The batches produced with lower proportions of polymer (4:1 drug-to-polymer ratio) displayed lower process yields. The better yield recorded at higher polymer proportions (F1 to F4) is likely a result of better entrapment of the drug in the polymer matrix and minimized processing loss. Generally, as the concentration of polymers increased, the percentage yield was found to significantly increase (p<0.05) (Figure 2A) for all the polymers studied. However, the studies indicated that the type of polymer employed did not significantly (p > 0.05) affect the process yield. The studies indicated that the selection of the proportion of drug to polymer was crucial for maximizing the process yield. The key observation during the formulation of SRSDs is that the process was quick, and product recovery was never an issue, unlike many of the complex microencapsulation procedures.

Optical microscopy is a simple and effective method utilized to examine the PS and surface characteristics of pharmaceutical formulations. It is well documented that most of the polymers tend to act as antinucleating agents, which therefore inhibit crystallization.[35,40] The reduction in the PS was noted at higher ratios (1:1), irrespective of the nature of the polymer used, suggesting the dominant effect of polymer concentration in controlling the nucleation and growth processes during solvent evaporation. It was noted that significantly lower (p<0.05) PS was observed at higher proportions of polymers (1:1) as in formulation F1 to F4, compared to the SRSDs produced with lower proportions of polymer (2:1) as noted with F5 to F6 (Figure 2C).

SEM calibration was verified by using a gold-coated standard, and sample stubs were sputter-coated with a consistent gold film thickness (approximately 10 nm) to ensure repeatable imaging. SEM is an advanced visualization method used to study the surface morphology and topography of pharmaceutical formulations at high magnification.[41] SEM provides valuable insights for SRSDs, providing information about particle shape, surface texture, and PS distribution.[42] These morphological features can influence drug release behavior and stability. The crystalline nature of COZ has been reported in studies undertaken earlier, endorsing the present observations.[28] Thus, SEM clearly indicated the morphological changes induced during the formulation.

A significantly higher (p<0.05) amount of COZ was found to be loaded at higher proportions of polymers compared to the SRSDs produced with intermediate (2:1) and lower proportions (4:1) of polymers, making them equivalent for drug loading consistency. It is likely that SRSDs with higher polymer proportions (1:1) would entrap higher (p<0.05) amounts of COZ in contrast to those produced with lower proportions of polymers (Figure 2B). Similar results have been obtained in our earlier studies when diclofenac was incorporated to produce SRSDs using sustained-release polymers.[43] The drug has more scope to disperse uniformly in SRSDs when higher proportions of polymers are used. It is likely that the solubility of the COZ in the polymer determined the percent drug loading. A better drug loading would be recorded in case of the good solubility of COZ in the polymer.[44] However, in the present study, no significant differences in drug loading were observed between different batches produced with different polymers.

DSC instrument calibration was performed using high-purity indium metal standards, verifying both onset temperature and melting enthalpy with a heating rate of 10°C/min under a nitrogen purge to ensure precise temperature control and enthalpy measurement. DSC is a thermo-analytical method used to monitor heat flow related to physical changes in a substance, including melting, crystallization, and glass transition events.[45] The DSC peak of COZ corresponded well with the reported melting point of COZ.[28] This well-defined peak shows the high purity and thermal stability of pure COZ. The shift and broadening of the melting point when evaluated against the COZ possibly suggest the solubility of COZ in the polymer at elevated temperature during recording of DSC, which eventually decreases the drug crystallinity. The absence of a melting peak indicates the complete loss of crystallinity.[46] This suggests that the drug has been converted into its amorphous form in SRSDs, which indicates molecular dispersion within the COZ in the polymer matrix during the preparation.

XRD calibration was executed using a silicon standard to confirm peak position accuracy and instrument resolution; samples were finely powdered and uniformly packed on sample holders to provide consistent diffraction patterns. XRD is an analytical method used to distinguish between crystalline and amorphous materials with the atomic arrangement of the sample.[39] XRD is particularly a valuable tool for assessing changes in crystallinity, which in turn can influence the solubility and bioavailability of drugs.[47] The intensity of the XRD pattern confirms COZ's highly crystalline nature. The XRD peaks noticed were found to agree well with the characteristic peaks reported in XRD diffractograms of COZ.[48] XRD patterns indicate the crystallinity of COZ but with reduced intensity compared to pure COZ, suggesting partial crystallinity of the drug in the physical mixture. This progressive decline in peak intensity and number of high-intensity reflections indicates a considerable reduction in crystallinity. Quantitatively, the crystallinity of COZ decreased from 100% in the pure state to 62.58% in the physical mixture and 60.92% in the formulation. These results confirm a successful transformation of the crystalline nature of COZ to a semicrystalline form, which is likely to be advantageous for retarding drug dissolution and drug release efficiency.[49]

The data obtained helps in anticipating the drug's *in vivo* performance and ensuring consistent therapeutic effects. The higher proportion of the polymer, leading to stronger interaction with COZ, could explain the incomplete release in 8 h. Two-way ANOVA followed by Tukey's post hoc test was effectively used to analyze the drug release data, allowing multiple pairwise comparisons while controlling the family-wise error rate and providing statistically robust identification of significant differences among formulations. Figure 6 shows the drug release data presented as means±standard deviation (n=3, independent experimental replicates), ensuring reliability and reproducibility of the results as per reviewer recommendations. The formulations F1 to F4 that were produced with to polymer ratio of 1:1 demonstrated an incomplete release over a span of 8h. Among all, formulation F5 containing Eudragit RS100 produced using a drug-to-polymer ratio of 2:1 was found to display a sustained yet near-complete release of 78.11±6.18% in 8 hr with minimal burst release (29.97% at 1 hr). The difference in drug release between F5 and F1-F4 was highly significant (p<0.05). In contrast, when the drug-to-polymer ratio (4:1), as in the case of F7 and F8, the SRSDs failed to control the release, as these formulations resulted in an initial burst release. The sustained release seen in F5 is attributed to the poorly permeable nature of RS100, which is likely to form a dense matrix that results in controlled drug diffusion. Eudragit RS 100 is a pH-independent sustained-release polymer having low permeability.[49] Moreover, the semicrystalline nature of COZ in the polymer matrix would account for the sustained release from F5. On the contrary, Eudragit RL100 is a swellable polymer with higher permeability, which may explain the burst release observed in F7 and F8. The burst release in F7 and F8 was significantly higher compared to that of F5 (p<0.05). Overall, F5 appeared to be the ideal formulation for achieving sustained drug release with minimal burst effect. The release profile of COZ-SRSDs (F1-F8) was modelled as per Higuchi, Korsmeyer-Peppas, and First-order models. Overall, the type of polymer and polymer concentration critically govern COZ release, with higher ratios enhancing matrix integrity and controlling diffusion. Among all the formulations, the formulation F5 appeared to be the most ideal batch with consistently high R^2 values across all models. The drug release profile of formulation F5 followed first-order kinetics and was best described by the Higuchi diffusion model. In addition, drug release from the batch followed anomalous transport as per the Korsmeyer-Peppas equation. The drug release is likely to happen in three steps: the first involves diffusion of the media into the matrix, followed by dissolution of the drug in the media. The drug solution thus formed is finally known to diffuse out of the polymer matrix. The drug-depleted zone is likely to form a ghost matrix, as indicated in the schematic illustration represented in Figure 7. Thus, the studies conclusively indicated that F5 emerged as the ideal formulation for achieving consistent, sustained, and near-complete drug release of COZ.

CONCLUSION

The study successfully developed COZ-SRSDs using the solvent evaporation technique. The SRSDs were found to display good flowability and compressibility. The solid dispersions formulated using Ethyl cellulose, Eudragit RL100, and Eudragit RS100 displayed sustained drug release. Among the eight formulations, F5 with Eudragit RS100 (50 mg) exhibited minimal burst release at the initial 1h, and sustained drug release over 8 hr. Drug release kinetics followed first-order and Higuchi diffusion models, indicating concentration-dependent, diffusion-controlled release. The Korsmeyer-Peppas model confirmed Fickian diffusion,

ensuring controlled drug delivery. This study presents a viable strategy to ensure a sustained yet complete drug release of drugs that exhibit poor solubility and short half-life. The bottom-up technique adopted for the development of sustained-release solid dispersions appears to be feasible, scalable, and well-suited for commercialization. A comprehensive study pertaining to stability, process scale-up, validation, and manufacturing feasibility assessments is to be undertaken to establish the commercial viability of these formulations and ensure consistent product quality at an industrial scale. A key limitation of this study is the lack of *in vivo* evaluation. Although the *in vitro* results demonstrate promising sustained-release characteristics, *in vivo* studies are critical to comprehensively assess the formulation's translational potential, pharmacokinetic behavior, and therapeutic efficacy. Future investigations will focus on addressing this gap to confirm the clinical relevance of our findings.

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ABBREVIATIONS

COZ: Chlorzoxazone; **ASDs:** Amorphous solid dispersions; **SRSDs:** Sustained release solid dispersions; **nm:** Nanometer; **PBS:** Phosphate buffer solution; **h:** Hours; **cps:** Count per second; **DSC:** Differential scanning calorimetry; **XRD:** X-ray diffraction; **SEM:** Scanning electron microscopy, **CI:** Carr's Index, **AOR:** Angle of Repose, **HR:** Hausner's Ratio.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

This study explored COZ-SRSDs, a muscle relaxant with a short half-life, to enhance its therapeutic efficacy and reduce dosing frequency by oral route. SRSDs were prepared using the bottom-up solvent evaporation method with various polymers, showing excellent micromeritic properties and high drug loading and yield. Characterization techniques confirmed reduced crystallinity and maintained drug integrity. *In vitro* release profiles showed prolonged drug release over 8 hr, with batch F5 demonstrating optimal performance, following first-order kinetics and Fickian diffusion. The approach offers a practical and scalable strategy for developing sustained release formulations of COZ.

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