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Formulation and In-Vitro Evaluation of Polymer-Based Extended-Release Pellet Tablets of Diltiazem

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Abstract: An important development in cardiovascular health is the creation of a blood pressure-lowering extended-release formulation. With this novel method, antihypertensive medications are released gradually and continuously, ensuring ideal blood pressure levels all day long. Reducing the frequency of medicine administration improves ease for patients and adherence, which has a positive impact on long-term results. The regulated distribution technique used in this formulation not only increases efficacy but also reduces the possibility of adverse effects, improving patient comfort and overall quality of life. The extended-release formulation has the potential to revolutionise the treatment of hypertension by providing people with high blood pressure with a more effective and secure option. The main objective is to formulate an Extended-release formulation to lower BP, which improves patient compliance, reduces the dose frequency, and minimizes the fluctuations seen by immediate-release tablets, which require multiple dose administration throughout the day. Diltiazem (DTZ) of Extended-release pellet tablets was formed by using Wurster Coater Granulator to load and coat the pellets with the drug using different polymers, and the Pre-formulation study was carried out. To check the compatibility of DTZ with other polymers, a DSC and FTIR study was carried out to make pure and more stable formulations. The pellet tablet products' dissolution profile and physicochemical parameters are compared. DTZ of extended-release pellets in-vitro dissolution study was done using pH 4.5/ 6.8 phosphate buffer using USP-2 type method for 2, 3, 4, 6, 8, 12, 18, 24, and 30 hrs. For the drug release profile, significant differences were checked for different formulations. The highest release rate of drug retarding was shown by those with higher polymer content. DSC and FTIR carried out the characterization of DTZ to check the compatibility of the drug with polymers or not. The stability study was carried out for different months to develop a stable formulation. It was concluded that DTZ of Extended-release pellet tablets helps treat hypertension by releasing the drug throughout the day for 30 hours. It helps in lowering BP and prevents various cardiovascular complications.

Keywords: Eudragit, Extended-Release Pellet Tablets, Dissolution Profile, Release Kinetics, Drug Layered, Stability Study.

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1. INTRODUCTION

Polymer-based extended-release (ER) pellet tablets are an effective approach designed to release the drug for an extended period to develop a safe drug delivery dosage form that improves patient compliance and reduces the dose frequency. The pellets are enclosed by the use of matrix polymer or are coated into a tablet .[1] This polymer matrix helps increase the drug's prolonged release by regulating the drug's diffusion profile as a controlled release. Ethyl cellulose, Eudragit, and HPMC are various polymers used for ER matrix. [2,3] The techniques of enclosing into a matrix polymer or coating and selecting polymers play a vital role in enhancing the release profile and dissolution of the drug. [4] This study's main need is that the drug's biological half-life (DTZ) is short. Hence, patients are advised to take it regularly every 6-8 hours.[5] So, using immediate-release or other conventional dosage forms requires multiple administration doses, which causes fluctuations in plasma drug concentration or blood levels.[6] Hence, to cure it, there is a need to formulate an extended-release formulation for the drug to improve the safety and efficacy of the drug for the treatment of hypertension.[7] This increases the absorption of the drug, thereby improving the bioavailability as pellets move freely in GIT Tract. The main objective is to formulate the ER pellet, which releases the drug for over 30 hours; this helps reduce the dose frequency and improves patient compliance for the treatment of hypertension.[8] Ghadge et al., 2013 have developed DTZ formulation by an extrusion method and discuss various parameters like type of polymers and concentration of variables on the release profile of pellets to formulate an optimized formulation.[9] B Sudheer, V Ramana1, et al., 2019 formulated DTZ HCl pellets and showed the successful preparation of sustained-release pellet tablets for wet granulation technology.[10] DTZ is a slow channel blocker and cardioprotective agent and is a category of anti-hypertensive. It depressed the conduction of the A.V node, thereby decreasing the heart rate. It increases the overall blood flow, mainly in the coronary arteries (epicardial region), acting as a potent vasodilator.[11] Hypertensive individuals mainly experience the Anti-hypertensive effect. In contrast, only a minor fall in BP is seen in a normal individual as the degree of hypertension is directly proportional to the magnitude of BP reduction .[12] DTZ showed that it mainly could decrease the oxygen demand of the myocardial and thereby helps in increasing exercise tolerance activity. [13] It causes very little negative inotropic effect by causing dilation of coronary arteries (large and small) both and produces coronary smooth muscle vascular relaxation at all drug levels. The result causes a reduction in peripheral resistance and decreases systemic blood pressure. This further results in an increase in epicardial blood flow of coronary. [14]The physical property of DTZ of extended-release pellets is that they have a bitter taste, are white crystalline in nature, and are soluble in water. [15] The development of extended-release pellet tablets of the consistent dosage form of DTZ by providing a sufficient drug consistently with time. ER, pellet drugs help improve the efficacy and safety of dosage form. It also produces a flexible dosage form of design. [16] The major advantage of the Extended dosage form of pellets is that there is less chance of dose dumping than in other dosage forms. They mainly increase the overall absorption of the drug, thereby increasing the bioavailability as pellets move freely in the GI tract. [17] The main objective of this study is to formulate an ER formulation of DTZ that helps reduce the dose frequency, side effects, and fluctuations seen by other immediate-release dosage forms.[18] These results help further study develop an ER formulation to improve the product's efficacy and enhance patient compliance. The main aim is to study the in-process parameters during DL coating by identifying the CQAs and CPPs to develop an optimized and stable formulation to release the drug throughout the day for 30 hours.

2. MATERIALS AND METHODS

2.1. Materials used

DTZ was taken from Sun-Pharmaceutical, Eudragit S 100, Tri-ethyl citrate, Purified Talc, Isopropyl alcohol, Acetone, and Purified water from Sun-Pharmaceutical industries limited, Mohali (Punjab).

2.2. Pre-Formulation

Pre-formulation study was done to check the physical /chemical characteristics of the DTZ with excipients. For the effective dosage form, it is considered a rational step.[19]

2.2.1. Tapped density, Bulk density

The powder was evaluated for Tapped density, Bulk density, and Particle Size Distribution. It was calculated by the weight of the powder, which is tapped for 100 stokes using bulk density apparatus.

2.2.2. Particle Size Distribution

For the powder, the particle sifter checked the vibro size using mesh size 14-30 according to the ASTM sieve.[20]

2.2.3. Drug Excipients Compatibility Studies

To check the compatibility of DTZ with other polymers and excipients, Drug-Excipients Compatibility Studies is carried out. The main part of this study is to maintain the quality of drug products from the presence of inactive substances that can degrade the product. The ratios of excipients with drug substances are carried out by HPLC analysis with the use of binary mixtures of an appropriate percentage of its composition. The DTZ was mixed with different excipients in the ratio 1:1 and kept at 40 °C / 75 % RH and 4 °C (as positive control) for 1 month and 3 months. [21]

2.3. Analysis by UV Spectrophotometer

To prepare a calibration curve of DTZ by UV, a stock solution of DTZ with a known concentration is prepared using a solvent such as methanol or water. A series of working standard solutions with different concentrations of DTZ are used with stock solutions. The absorbance of all stocks was calculated at a particular wavelength using a UV spectrophotometer. A calibration graph is then plotted between absorbance values and standard solutions' corresponding concentrations. Different dilutions were made to form the stock solution concentration (5,10,15,20,25, and 30 µg/ml). The absorbance was set at 237 nm .[22]

2.4. Formulation of Extended-Release Pellet Tablets

Before fitting the gun to the Wurster bowl, adjust the speed of the peristaltic pump to the flow rate of 60-100 g/min. Ensure the silicone tubing product should be dipped inside dispersion during the whole process of spraying. The

optimum length of silicone tubing to be used to avoid curve uniformity of flow and to maintain towards guns .[23] Take a quantity of dispersion required for 18 % weight build-up separately in a suitable container and carry manual stirring / use suitable mechanical stirrer to avoid settling of talc in dispersion.[24] Ensure continuous spraying before loading the pellets into a bowl. Continue stirring of dispersion during coating. Load the Drug Layered (DL) pellets into the bowl of the Wurster Granulator by keeping the lid over the column and adding DL pellets along the periphery of the bowl. After pre-warming, start coating with dispersion. Record parameters after achieving desired inlet temperature.[25] Drug layered pellets to achieve the product (bed) temperature NMT 55 °C by setting parameters and, after achieving cool pellets to get product temperature (24-32 °C) .[26] Table 1 Indicates the batch-wise composition of pellet formulation.

Table 1: Record details of dispensed materials Batch wise Composition.

Sr.no	Material	Unit Quantity (mg)	Batch Quantity (kg)
1.	DTZ	30	33.990
2.	Eudragit	3.89	4.589
3.	Triethyl citrate	0.232	0.458
4.	Talc USP	1.34	2.294
5.	Isopropyl alcohol	q.s.	38.323
6.	Acetone USNF	q.s.	24.448
7.	Purified Water USP	q.s.	3.304
	Total	35.462	107.406

q.s. = quantity sufficient

Table 1 illustrates the composition of raw materials. In a suitable container equipped with a mechanical stirrer, take purified water USP (3.304 kg). To the above-purified water, add isopropyl alcohol (43.546 kg) and acetone (37.260 kg) to form a diluent and stir continuously to form a diluent mixture. Divide the diluent mixture into two equal parts. Take part 1 and slowly add Eudragit S (4.690 kg) with continuous stirring to ensure no lumps are formed and dissolve it completely. Add slowly to part 2, continuously stirring at high shear, and add talc (2.333 kg). Slowly add Tri-ethyl citrate (0.582 kg) under stirring for 30 min. to the above mixture, stirring it with high shear. Pass the above dispersion through a #250-micron sieve and filter it. [27] After ER Coating, start air drying of ER Coated pellets as per process parameters. After Air Drying, dry ER Coated Pellets until desired product temperature is achieved with the set process parameters in Wurster Coater Granulator. (Table 5) indicates the set parameters of the Wurster Coater Granulator. Record drying parameters once desired inlet temperature is achieved. Cool the pellets till product temperature reaches NMT 30 °C and record the observations. Collect dried pellets in double-lined polybags duly labeled suitable containers and record weight. The calculation for weight build-up and dispersion required for further spraying. If weight build-up is achieved within the 18 ± 1% w/w limit, then proceed to an additional drying process. If weight build-up is less than 17% w/w, then again start ER Coating with the calculated quantity of dispersion coating till weight build-up is achieved and record the in-process parameters. (Table 6) indicates the in-process parameters observed during DL coating). Cool the pellets till desired product temperature is reached. Sift the unloaded ER release pellets through Vibro Sifter fitted with a 1204 or 850-micron sieve to remove fines and record the processing time = 20 minutes.[28] Discard the oversized agglomerates from the #1204 microns sieve and take the undersized ER Pellets for further sifting by passing through the #850 microns sieve. This sifted material gets collected into a double polybag duly labeled suitable container.[29] Critical Quality Attributes (CQA) are defined according to the FDA as applying to any product's physical, biological, or chemical characteristics that must be within a particular limit to maintain the required quality of finished goods. It is considered the first step of process validation during the process's design stage, and all data must be maintained.

2.5. Characterization of ER Pellet Tablets

2.5.1. Differential Scanning Calorimetry (DSC) Analysis

DSC is used for thermal analysis of drugs and excipients. It measures the heat flow concerning temperature by heating the tablet. It provides the drug's thermal behavior and information related to a glass transition temperature and melting point.[30]

2.5.2. Fourier Transform Infrared Spectroscopy

FTIR spectroscopy is used for qualitative and quantitative analysis of tablets. We record the infrared spectrum by placing the tablet in a sample holder. It is used for drug-excipient interactions with the tablet. It provides information about the presence of impurities or the presence of chemical bonds between drugs and excipients.[31]

2.5.3. In-vitro Dissolution study of ER Pellets

Dissolution was carried out on USP Type 2 apparatus using 900 ml of pH 4.5 / 6.8 phosphate buffer solution, which rotated at speed (50 rpm) and 37 °C for 2-30 hours. At intervals of every one hour, a 5 ml sample from the medium of dissolution was withdrawn, and to further maintain this volume, the fresh sample of the dissolution medium was replaced. After dilution and filtration, it was analyzed under UV Spectrophotometer at 237 nm for DTZ. The sample was tested by plotting the calibration curve of DTZ, and the equation after forming a straight line indicates how much drug is present in the sample. It indicates a clear image of the drug release profile under specific time intervals. A graph is plotted with the percent drug release versus time (hours). [32]

2.6. Stability studies

According to ICH guidelines, a stability study was carried out by DTZ. The formulations are kept at 40 °C / 75 % RH for 3 months.

3. RESULTS AND DISCUSSION

3.1. Pre-Formulation of Pellets

3.1.1. Physical description

The DTZ is typically tested by viewing it against a white background under specified lighting; it was observed that the DTZ was white crystalline powder. Table 2 indicates the observations of the physical characteristics of DTZ.[33]

Table 2: Observations of Physical Characteristics of DTZ.

Test	Observations	Results
Description	White, odorless crystalline powder or small crystals	Complies
Taste	Bitter	Bitter
Solubility	Freely soluble in chloroform, formic acid, methanol, and water, sparingly soluble in dehydrated alcohol, and insoluble in ether. Melts at about 210 °C with decomposition	Complies Melting point 211.3 °C
Specific Rotation (10 mg/ml, in water)	+110° to +116°	+115.4°
Loss on Drying (% w/w)	NMT 0.5	0.15
Residue on Ignition (% w/w)	NMT 0.1	0.076

Table 2 illustrates the physical characteristic of DTZ. DTZ is a calcium channel blocker used for the treatment of hypertension. It appears as a white crystalline powder in its solid form. Its solubility is that it is freely soluble in water but does not dissolve completely in the medium. However, its solubility in organic solvents like methanol and ethanol is higher than in water. The molecular weight of DTZ is approx..450.97 g per mole. DTZ has a bitter taste and is odorless. The melting range of DTZ is 208- 213 °C. The specific rotation of DTZ can be calculated by noting the rotations of plane-polarized light. The ignition residue of DTZ is calculated by measuring the residue left behind after combustion. [34]

3.1.2. Bulk Density, Tapped, and Particle size distribution

Bulk density is calculated by the mass of the powder (DTZ) divided by the bulk volume, as shown in Table 3. It is also known as apparent density. Units are g/ml. Tapped density is defined as the powder density after it vibrates or is mechanically tapped to obtain uniformity. Particle size distribution refers to the size of particles present in the API of DTZ. It must be within a particular range for accurate flowability.[35]

Table 3 Observations of Bulk Density, Tapped, and Particle size distribution:

Parameters		Observations
		Lot
Bulk Density (g/ml)		0.755
Tapped Density (g/ml)		0.829
Particle Size Distribution	Sieve (#ASTM)	% Cumulative Retained Weight
	14	0
	16	0.395
	18	75.041
	25	99.736
	30	99.769

Table 3 illustrates the bulk density, tapped density, and particle size distribution results of DTZ. These results help identify the compressibility, uniformity, and flowability of the powder (API) of DTZ. The powder bulk density was 0.755 (g/ml). The tapped density of the powder of DTZ is found to be 0.829 g/ml. The particle size distribution of DTZ was carried by vibro sifter using different ASTM sieves, and the cumulative retained weight was observed. For sieve 16, 18, 25, and 30 sieves, the cumulative retained weight was 0.395, 75.041, 99.736, and 99.769 % respectively. [36]

3.1.3. Drug Excipient Compatibility Study

To check the compatibility with API, all the excipients are checked that are used in the final formulation. Samples were stored at 40 °C / 75 % RH for 3 months, as shown in Table 4 (a) and (b). The results showed no rise in impurities at each stage and different conditions. Therefore, all the excipients are compatible with the API at all conditions. [37]

Table 4 (a): Drug Excipients Compatibility Studies at Initial Stage

Stage Wise	Initial			
	Impurity			
	Impurity A	Impurity B	Impurity C	% Assay
API	N.D	N.D	BLOQ	100
API Hydro-Chloride Complex	N.D	N.D	0.01	99.8
Solvated API Hydro-Chloride Complex	N.D	N.D	0.01	99.9
ER Coated API Hydro-Chloride Complex	N.D	N.D	0.01	99.9

Table 4 (b): Drug Excipients Compatibility Studies at 40 °C / 75 % RH for 3 months				
Stage Wise	40 °C / 75 % RH (3 months)			
	Impurity			
	Impurity A	Impurity B	Impurity C	% Assay
API	N.D	N.D	BLOQ	100
API Hydro-Chloride Complex	N.D	N.D	0.01	99.8
Solvated API Hydro-Chloride Complex	N.D	N.D	0.02	99.7
ER Coated API Hydro-Chloride Complex	N.D	N.D	0.03	99.6

ND- Not Determined, BLOQ- Below Limit of Quantification

Table 4 illustrates the drug excipient compatibility study between polymers or excipients and DTZ. It is a very important study to ensure that these polymers or excipients do not cause interactions with the DTZ, which leads to poor efficacy and stability of the product. According to different temperature and humidity conditions, these excipients are selected, and any change or interactions are noted with that of DTZ. Conducting these studies is essential during the developing stage to ensure that the used polymers are compatible with the DTZ to develop a more stable product throughout its shelf-life. At 40 °C / 75 % RH for 3 months, samples were stored, and at each stage, it was found that there is no increase in impurities throughout and are in a limited range, concluding that DTZ is compatible with all excipients and polymers. [38]

3.2. Analysis by UV

The result shown in Figure 1 indicates a linear curve between concentration and absorbance with an r-value of 0.9987, indicating data as a good fit. [39]

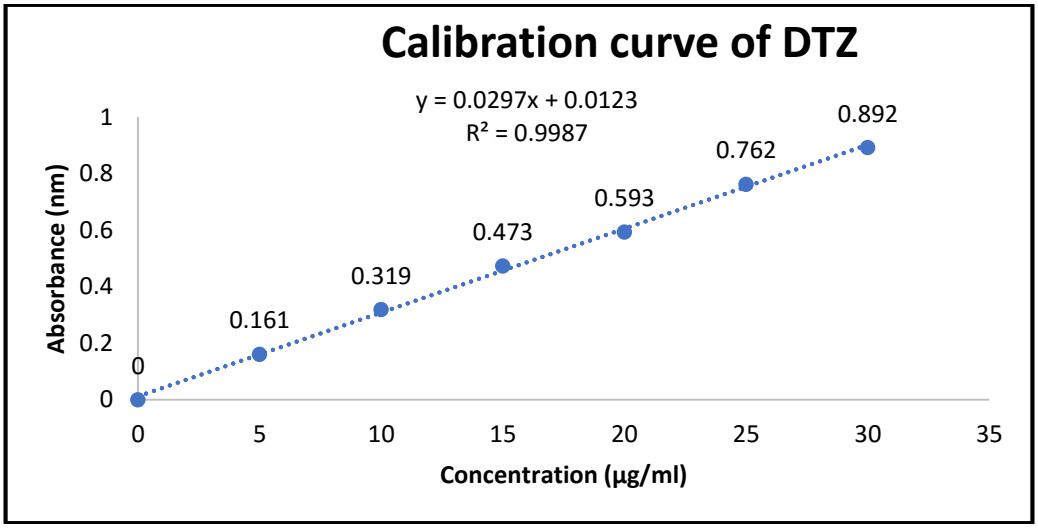

Fig 1: Calibration curve of DTZ

Figure 1 illustrates the calibration curve of DTZ prepared by the known concentration of DTZ as a standard solution and is analyzed by UV Visible Spectrophotometer. Absorbance is noted at different concentrations. On the x-axis, the concentration of DTZ is plotted, and on the y-axis, absorbance is plotted. This calibration curve helps determine the unknown concentration of the sample by using the calibration curve equation. For good fit and linearity, correlation coefficient parameters are evaluated. A linear relationship is desired for the calibration curve for effective results. [40]

Table 5: (Setting of Wurster Coater Granulator Parameters)	
No of Guns	1
Nozzle diameter	1.5 mm
Base Plate	C / H
Guns to be fixed	HS Gun
Filter bag Porosity	Bonnet filter / 400 microns

Table 5 illustrates the parameters of the Wurster coater granulator. HS gun with 1.55 mm nozzle with C/H Base plate to be used for all stages of ER Coating process. Check finger bag assembly for proper fixation before use. Check the gun's functionality before setting it up and ensure that "O" rings are properly set, and there is no back pressure from the gun's nozzle. Check that atomization air tubing is properly fitted with gun assembly. If the gun is blocked during spraying, it shall be cleaned with isopropyl alcohol to remove the adhesive polymer and restart the process. Ensure continuous spraying before loading the pellets into the bowl. Continue stirring of dispersion during coating. Whenever required (observing higher filter bag DP values), clean or change filter bags after spraying each lot. [41]

Table 6: IN-Process parameters observed during DL coating (1-9)

Parameters	Value	Observations								
In-process (IP)	Range	IP1	IP2	IP 3	IP 4	IP 5	IP 6	IP 7	IP 8	IP 9
Inlet temp (°C)	30-40	31.7	31	31	31.1	31	31.2	32.1	32	32
Product temp (°C)	20-40	30.2	29.7	39.2	29.2	29.2	29.2	29.7	29.6	29.5
Exhaust temp (°C)	26-30	28.1	27.2	26.7	26.5	26.4	26.7	26.8	29.6	29.5
Blower Drive (%)	70-90	79	78	80	79	80	79	84	84	83
Absolute humidity (g/kg)	9-11	9.2	10.4	9.7	9.7	9.8	9.8	10.1	10.1	10
Atomization air pressure (Bar)	3	3	3	3	3	3	3	3	3	3
Inlet airflow (CFM)	640-690	653	650	649	659	652	650	650	678	687
Initial wt. of coating solution (kg)	70-100	96	94.2	92.3	90.2	88.1	86	83.75	81	78.45
Wt. of coating solution after 5 Min (kg)	70-100	95.7	93.9	91.95	89.85	87.75	85.65	83.3	80.65	78
Initial wt.-wt. After 5 Min (kg)	0.30-0.50	0.30	0.30	0.35	0.35	0.35	0.35	0.45	0.45	0.45
Spray rate (g/min)	60-100	60	60	70	70	70	70	90	90	90

Table 6 illustrates the in-process parameters to be observed during Drug-layering coating. All parameters must be monitored critically, like nozzle diameter, Air displacement plate, Column height, Inlet temperature, Blower drive, Product temperature, Atomization air pressure, Inlet air flow, Spray rate, and Inlet RH. Drug layered pellets to achieve the product (bed) temperature NMT 55 °C by setting parameters and, after achieving, cool pellets to get product temperature (24-32 °C). Collect dried pellets in double-lined polybags duly labeled suitable containers. [42]

3.3. Characterization

3.3.3. DSC

DSC is used for the thermal analysis of DTZ with other polymers to check the compatibility, as shown in (Figure 2). A sample of DTZ is placed in a sealed aluminum pan, and heating is provided. For the accurate measurement of heat flow, by the use of an empty pan baseline is generated. The change in the chemical and physical nature of DTZ is measured as we increase the temperature to evaluate the decomposition, melting point, etc. By evaluating these parameters, the DSC instrument will generate a thermogram. A graph is plotted between the temperature on the x-axis and heat flow on the y-axis. By generating endothermic and exothermic peaks, we can easily analyze the melting point of DTZ. [43]

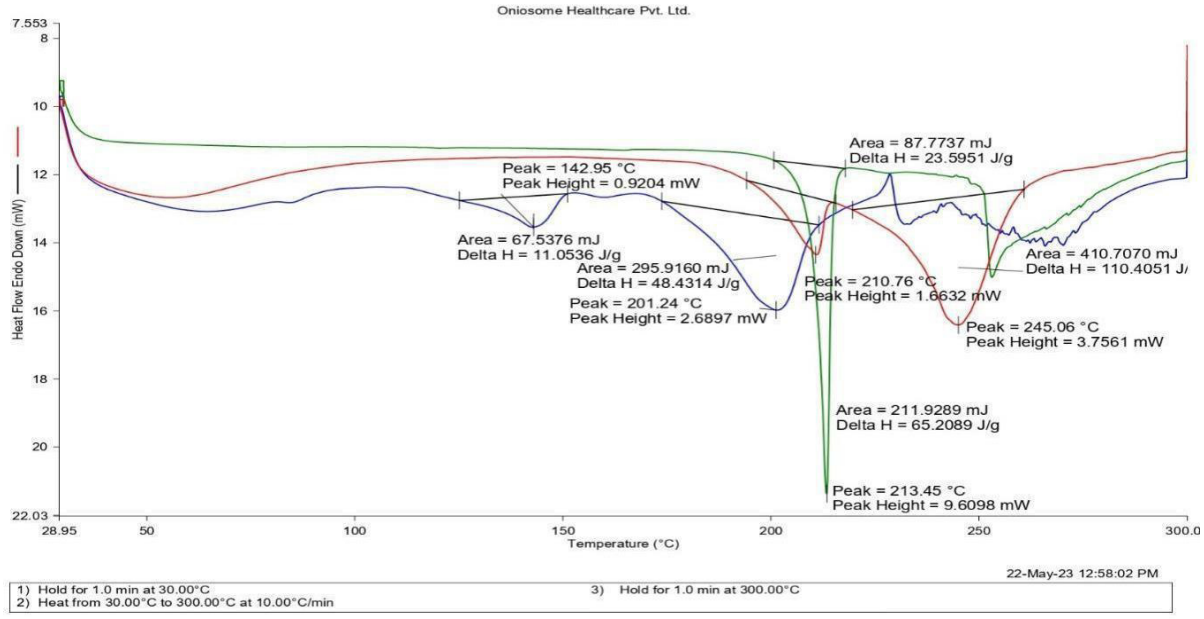

Fig 2: DSC analysis of DTZ with other polymers showing the melting point at 213.45 °C.

Figure 2 illustrates the analysis of the DSC of DTZ with other polymers to check the compatibility. Thermal analysis was performed on the pure DTZ and polymers to check the thermal behavior using a Differential Scanning Calorimeter of (Perkin-Elmer-I 6000). Scanning was performed at 30 to 300 °C at a heating rate of 10°C/min under a nitrogen atmosphere. The sample withdrawn was 3.720 mg and sealed in an aluminum pan. The thermogram of DSC showed a sharp endothermic peak at 213.45 °C of pure DTZ. It indicates the melting point of the DTZ. Other peaks in the thermogram indicates that the DTZ is pure and compatible with other polymers. [44]

3.3.4. FTIR

Fourier Transform Infrared-Spectroscopy is used to identify the presence of functional groups by determining the compound's molecular structure. When we placed our

sample DTZ into it, there was a formation of characteristic peaks, as shown in Figure 3, of different wave numbers, which provide information on which type of functional groups are present and their chemical bonds. In our sample of DTZ, we found different functional groups like carbonyl group C=O, N-H group, C-O-C ether bond stretching vibrations, and C-H aliphatic stretching. [45]

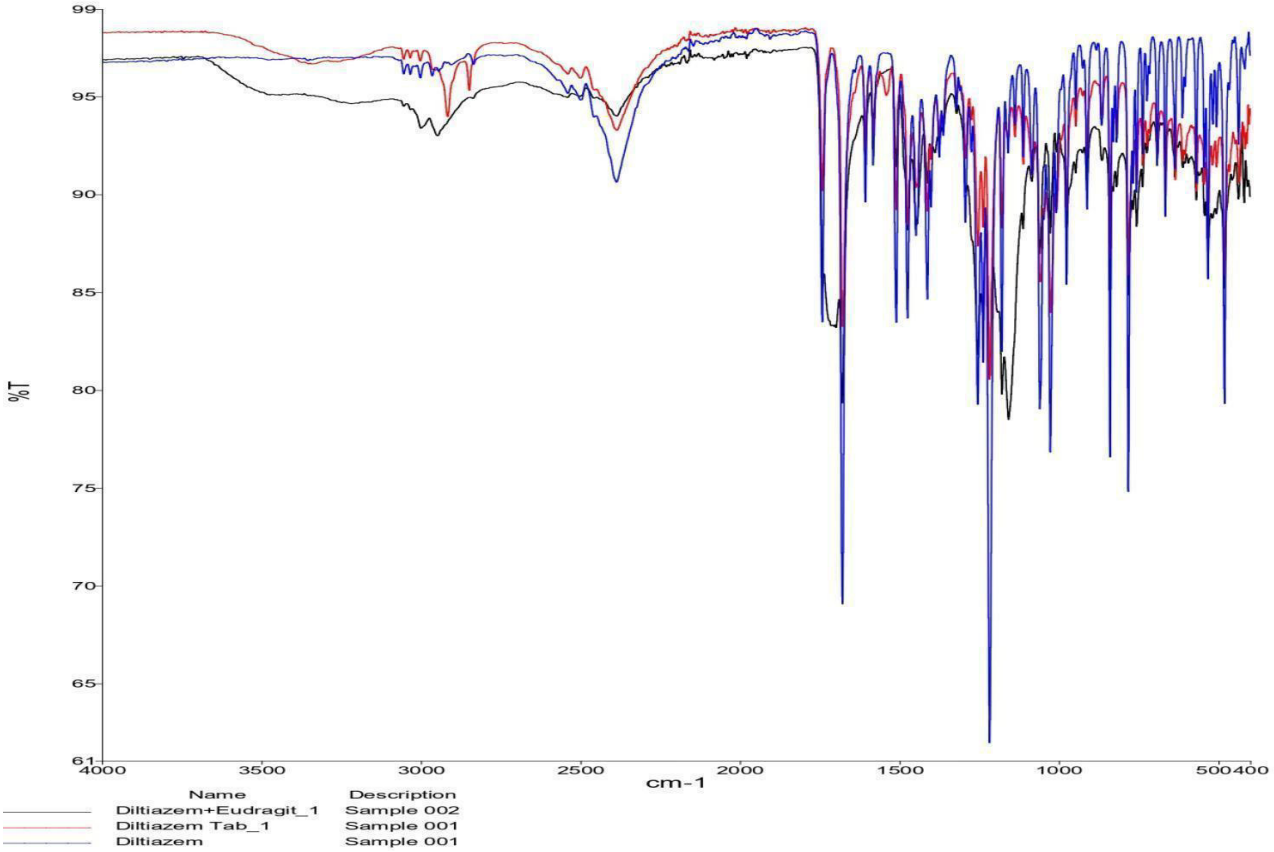

Fig 3: FTIR Spectra of pure DTZ with polymers showing the presence of functional groups.

Figure 3 illustrates the FTIR spectra of DTZ with other polymers. To evaluate the compatibility study of DTZ with polymers, an FT-IR study was conducted by Perkin-Elmer spectrum two FTIR apparatus. The spectra of FTIR shown in characteristic peaks at 2950.67 cm^{-1} (aliphatic C-H stretching), 2388.60 cm^{-1} NH stretching, amine), 1743.04 cm^{-1} (acetate C=0 stretching), 1680.43 cm^{-1} (Lactam C=0 stretching), 839.60 cm^{-1} (O substituted aromatic C-H stretching and 782.03 cm^{-1} (p- substituted aromatic C-H stretching). It indicates no drug-polymer interaction with DTZ, which shows the consistent quality of the final product. [46]

3.4. In-vitro Dissolution Study of DTZ in different Dissolution media

A dissolution study was conducted on USP Type 2 apparatus by using 900 ml of 0.1 N HCl, pH 4.5 / 6.8 phosphate buffer solution at 100 rpm speed and temperature to be set at 37 °C as shown in Table 7. [47] At an interval of every one hour, 5 ml sample from the dissolution medium was taken off and to further maintain the quantity of volume, the dissolution medium was replaced with the fresh medium. After dilution and filtration, it was analyzed under UV Spectrophotometer at 237 nm for DTZ. The sample was tested by plotting the calibration curve of DTZ, as shown in Figure 1. The formulation was best fitted in the first order of release kinetic model, and the r square is 0.9674. [48] A graph was plotted between the percent drug release and time, as shown in Figure 4.

Table 7: Dissolution Rate Profile (PB = Phosphate Buffer, DM = Demineralized Water)

Media	Time (hours)	2	3	4	6	8	12	18	24	30
0.1 N Hcl,900 ml	USP-2, 100 rpm	0	9	34	38	48	62	80	90	95 %
	USP-2, 200 rpm	2	10	36	41	43	62	86	95	99 %
	USP-2, 15 rpm	3	11	38	43	45	69	85	94	100 %
PB, pH 4.5, 900 ml	USP-2, 100 rpm	3	9	36	43	45	73	84	91	98 %
PB, pH 6.8, 900 ml	USP-2, 100 rpm	2	7	33	41	43	74	88	93	98 %
DM Water, 900 ml	USP-2, 100 rpm	3	9	36	43	44	70	85	94	101 %

Table 7 illustrates the in-vitro dissolution profile of DTZ. It states that at controlled conditions, how much rate of the drug gets dissolved from the active dosage form. It's a very important factor that can influence the drug product's effectiveness, bioavailability, and drug release profile. The dissolution testing is carried out in USP-II Paddle type apparatus using different dissolution media of 0.1 N HCl, Phosphate Buffer of pH 4.5, 6.8, and in demineralized water in

900 ml. The testing is performed at 37 °C temperature and different rpm of 15-200. It showed that in the case of 0.1 N HCl, 100 % drug was released and found to be more stable as DTZ is more stable in an acidic environment. While in other cases also, 95-98 % of drugs released showed better stability of DTZ in each case at different time intervals of up to 30 hours.[49]

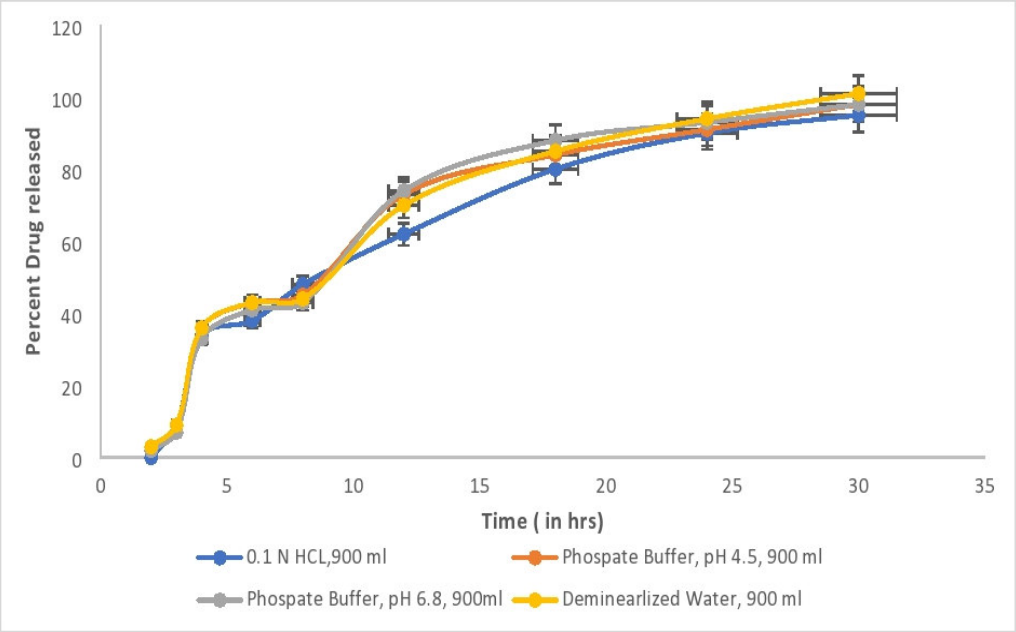

Fig 4: Describe the % drug release of DTZ

Figure 4 illustrates the graph of the percent drug release profile of DTZ at different media. On the x-axis, time is plotted, while on the y-axis, the percent drug release is plotted. At an interval of every hour, a 5 ml sample from the dissolution medium was taken off, and to further maintain the quantity of volume, the dissolution medium was replaced with a fresh one. Results showed that in the case of 0.1 N HCl, DTZ is more stable compared to other media as 100 % percent drug was released after 30 hours. [50]

3.5. Drug Excipient Stability Study

After 3 months, they are analyzed for drug content and physical appearance, as shown in Table 8 and Table 9. After 3 months, it shows no change in the formulation's drug content and physical appearance. Hence, it indicates a good shelf life and stable nature of formulation.[51]

Table 8: Drug-Excipients Stability Study

S.no	DTZ + Excipients	Initial	40 °C / 75 % RH	
			1 Month	3 Months
1.	DTZ (1:1)	white powder	No change occurs	No change occurs
2.	Ethylcellulose 20 cps (1:1)	white powder	No change occurs	No change occurs
3.	Talc (1:1)	white powder	No change occurs	No change occurs
4.	Microcrystalline cellulose (Avicel PH 102) (1:1)	white powder	No change occurs	No change occurs
5.	Aerosil (1:1)	white powder	No change occurs	No change occurs
6.	Eudragit (1:1)	white powder	No change occurs	No change occurs

Table 8 illustrates drug-excipients stability studies of DTZ to check its physical, microbiological, and chemical stability at conditions of 40 °C / 75 % RH for 1 and 3 months. These studies are essential to evaluate products' storage nature and shelf-life. Long-term stability studies and accelerated stability studies can be conducted at elevated temperatures. The compatibilities of different excipients used are checked against DTZ to evaluate their stability and compatibility with developing an effective formulation. After 1 or 3 months, the data evaluated for stability are to check any change in physical attributes, rate of degradation, and estimate expiration period and storage conditions by getting an idea about the drug's shelf-life. It showed no change in any effect of the formulation. Hence, it indicates a stable nature of DTZ. [52]

Table 9: Stage-wise drug: excipients composition for stability studies

Sr. No	Stage-wise Drug: Excipients composition	Ratio
1	DTZ	….
2	DTZ Hydrochloride	1:2
3	DTZ Hydrochloride complex (DTZ + Eudragit +isopropyl alcohol)	1:2:0.75

4	ER-coated DTZ Hydrochloride (DTZ +Eudragit + isopropyl alcohol + Talc + Tri Ethyl Citrate)	1:2:0.75:0.78:0.16

Table 9 illustrates the stage-wise drug-excipients composition for stability studies conducted by HPLC analysis. Appropriate composition of binary mixture percentage is chosen in the ratio of 1:1 of DTZ mixed with the excipients.

4. CONCLUSION

We prepared the ER pellet tablet by fluid bed Wurster coater in the study. Using the cause-and-effect diagram, the CQA affecting the release of the drugs is identified, and an optimized formulation was prepared. The drug is having short half-life and bitter taste, so frequent dosing is required. So, therefore there is a need to formulate the ER formulation to maintain the risk factors. It shows ER pellet tablets can effectively control blood pressure by releasing the drug throughout the day. It eliminates the risk of fluctuations seen with immediate release dosage form. It maintains the optimal level of the drug in the bloodstream. It reduces the risk of cardiovascular disease complications and maintains optimal levels of BP. By identifying the CQA, we see that the efficacy of ER is enhancing the drug release profile, and optimized products with fewer adverse effects are developed compared to conventional dosage forms. The research conducted in this study comprises the use of different coating techniques, the use of different excipients, and the techniques used in the pelletization process to achieve the desired drug release profile. This study describes and concludes the development and optimization of ER formulation, which has a greater importance for the early treatment of hypertension than other dosage forms. These results may help further research and development for developing ER dosage forms, which ultimately help increase efficacy and patient compliance.

5. FUTURE PERSPECTIVE

The ER formulation of pellet tablets prepared by Wurster Coater has greater importance in achieving the desired rate drug profile. But for further advancement, there are still chances to explore the field of ER formulation for future betterment in this area. The formulation of ER pellet tablets plays a vital role in treating hypertension. To increase the efficacy and safety of the formulation and to improve overall patient compliance, various research departments should focus on it for the betterment of the future. Advanced techniques of novel drug delivery systems like micro-encapsulation or the use of nanotechnology must be implemented for the development of ER pellet tablets for the treatment of hypertension to get the targeted site of delivery, improve the overall bioavailability and enhance the release kinetics of the drug. By using these techniques, there is less chance of dose dumping, reducing the frequency of dose and providing a controlled release of the drug. Future research on ER formulation must also be implemented in combination therapy as we know for the treatment of hypertension, multiple dosing administration is required to control the blood pressure at an optimal level. So, combination therapy is the other area that needs to be focused on to develop the ER formulation of multi-layered pellets, which encapsulates multiple drugs within a pellet for effective treatment and to improve the dissolution profile. For managing hypertension, personalized medicine is another approach to identify patients more likely to get treated using ER formulation. In this, various designs are studied to get accurate results for patients' benefit and decrease the overall side effects. To improve patient compliance, various patient-centric approaches must be used to treat hypertension using ER formulations. For the overall development and patient acceptance, future research must be incorporated to develop a friendly dosage form system such as pellets of taste masking or oral disintegrating tablets which can be easily taken by the patients as easy to use. It concluded that further research and improvement in this area could show desirable and promising results in the formulation of ER dosage form to develop a more efficacious product for overall stability and patient compliance to reduce the adverse effects.

6. AUTHORS CONTRIBUTIONS STATEMENT

Charul Rathore designed, planned, and edited the article. The data was collected and drafted by Sahil Arora.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

8. LIST OF ABBREVIATION

BP	Blood Pressure
DTZ	Diltiazem
ER	Extended Release
BLOQ	Below Limit of Quantification
CQAs	Critical Quality Attributes
HCl	Hydrochloride
DSC	Differential Scanning Calorimetry
FTIR	Fourier Transform Infrared Spectroscopy
RH	Relative Humidity
RPM	Revolutions Per Minute
NMT	Not More Than
USP	United State Pharmacopoeia
ASTM	American Standard Test Sieve Series
DL	Drug Layered

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