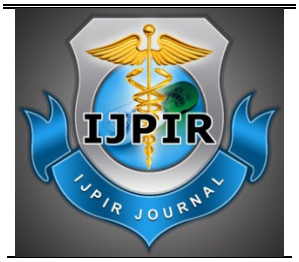
Research Article



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Characterization and Pre-formulation studies of Hydrochlorothiazide by using various analytical techniques

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ABSTRACT

The compatibility studies deal with the physical; chemical properties of Active ingredient (HTZ) with excipient binary mixture. The tasks for saturated solutions have carried out over the pH range of 1.2-6.8. The Solubility of Hydrochlorothiazide is about 0.08mg/L in the water at 37°C. Further, the solubility is not affected significantly (P > 0.05) in the buffer solutions in a pH range of 1.2 to 6.8. The PSD histograms represent the presence of Dv (50) 15.8 µm; Dv (90) 98.1 µm particles of Hydrochlorothiazide. From the p-XRD studies; the diffraction line profiles are 2θ values for diffraction peaks at 9.4979°, 19.0697° conforms to form A of Hydrochlorothiazide. By the UV-Visible; FTIR; NMR and Mass spectroscopy studies Characterized to Hydrochlorothiazide. The DSC thermo gram at 268.96°C represents the characteristic melting point of API. The Assay content results of Hydrochlorothiazide were within 99%-101%. Hydrochlorothiazide contains <0.5% impurities A, B, C, with >99.0%and all other unknown impurities has not detected in any of the drug substances. The compatibility of binary mixtures of drug and excipients stored at 40°C ± 2°C/ 75% ± 5% R.H. for one month has assessed and the % results of Assay and impurities from initial period to after 30th day does not have a significant difference; P< 0.01.

Keywords: Compatibility studies; DSC studies; NMR Studies; FTIR Studies; p-XRD studies

INTRODUCTION

Recent advances in novel drug delivery systems aim to improve the safety and efficacy of drug substances to accomplish better patient compliance. Even sustained-release formulations have investigated for the oral route of administration because of flexibility in designing dosage forms. Hydrochlorothiazide was selected considering into account their physicochemical, and biopharmaceutical properties. All recent clinical guidelines are still considered Thiazide diuretics are the primary treatment for the organization of hypertension[1]. The combination drug therapy at a lower dose h recommended permitting medications of different mechanisms of action, to complement each other and mutually effectively lower the blood pressure than the highest doses of the individual [2].

The primary intention of release drug delivery is to make sure safety and to improve the efficacy of drugs in addition to patient compliance [3]. The environment for drug diffusion and absorption varies along with the gastrointestinal (G.I.) tract. Based on these considerations, we have proposed a bi-layer tablet [4,5]. The pen west dynamically applies Geminex Technology in diabetes, cardiovascular diseases (CVD), cancer, and CNS disorders [6,7]. The polymeric bioadhesive bilayer tablets contain one layer with immediate-release /another with bioadhesive property [8,9].Hydrochlorothiazide is a 3,4-dihydro derivative of chlorothiazide. The chemical name is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, and its empirical formula is $C_7H_8ClN_3O_4S_2$. The molecular weight is 297.74g.mol-1, and its structural formula has represented in Figure 19. The oral dose of Hydrochlorothiazide is 65-75% bioavailable, with a

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Tmax of 1-5 hours, and a Cmax of 70-490ng/mL following doses of 12.5-100mg [10,11]. The oral LD50 of Hydrochlorothiazide is >10g/kg in mice and rats 12. The plasma half-life of Hydrochlorothiazide is 5.6-14.8h, and the renal clearance in patients with normal renal function is 285mL/min. Patients with a creatinine clearance of 31-80mL/min have an average renal clearance of 75mL/min, and patients with a creatinine clearance of ≤30mL/min have an average renal clearance of 17mL/min [13,14]. The most common symptoms have observed by electrolyte depletion, i.e., hypokalemia, hypochloremia, hyponatremia and dehydration resulting from excessive diuresis[15]. The physical state of the drug is white to off-white, or crystalline powder and slightly bitter taste [16,17]. It is soluble in ethanol at approximately 750g/L; in acetone, dilute ammonia; freely soluble in sodium hydroxide solution, n-butyl amine, dimethyl formamide; sparingly soluble in alcohol; insoluble in ether, chloroform, dilute mineral acids [16,18]. Hydrochlorothiazide is available as a generic drug under a large number of brand names, including Apo-Hydro, Aquazide, BPZide, Dichlotride, Esidrex, Hydrochlorot, Hydro Diuril, HydroSaluric, Hypothiazid, Microzide, Oretic, and many others[19]. (Figure 1)

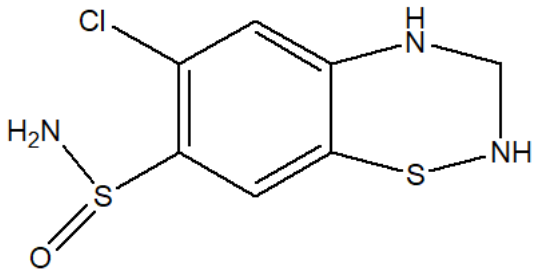

Figure 1: Typical Chemical structure of Hydrochlorothiazide

MATERIALS AND METHODS

Materials

Hydrochlorothiazide (HTZ) is gift sample from Amoli Organics Ltd, Mumbai, corn starch has procured from S.A. Pharma chem Pvt Ltd, Mumbai, MCC (Avicel PH 101); Crospovidone; PVP K-30, magnesium stearate, croscarmellose sodium, DCP and SSG are donated by SM Pharmaceuticals, Malaysia, and all other chemicals used were of analytical grade.

Methods

SolubilityStudies

It has conducted by using U.V. –Visible Spectrophotometer (Model: UV 2600; Make: Shimadzu). The Solubility of the drug (HTZ) has determined in distilled water, 0.1N hydrochloric acid pH1.2, 0.1N hydrochloric acid pH1.2 with 1% w/v sodium lauryl sulfate; acetate buffer pH 3.0, and 4.0, phosphate buffer pH 5.0 and 6.8, and 0.1N sodium hydroxide. A precisely measured volume of each solvent has poured in screw-capped glass vials followed by the addition of the excess drugi.e29.3mg/L to 436.3mg/L in 10ml of solvent. The glass vials were sealed and positioned on a mechanical shaker (Burrel Scientiphic wrist action laboratory shaker, Make: Fisher, Model: 75) at 37 °C for 24 hours. After that, aliquots were withdrawn, centrifuged, and filtered. The filtrates have diluted, and absorbance has recorded.

Particle size distribution (PSD)

It has carried out on Particle size analyzer (Model: Mastersizer 3000; Make: Malvern Panalytical Ltd). The laser diffraction technique has employed to measure the size distribution of powder particles in a dry dispersion apparatus. Based on distribution data, the particle size of powder has defined by various means like D (3, 2) D (4, 3), and maximum particle size measured percentiles are Dv10, Dv50, Dv90.

X-ray diffraction

The p-XRD pattern is a record of the diffracted intensity of a crystalline sample in one dimensional as a function of diffraction angle. The study has conducted on an X-ray diffractometer (Make: Malvern Panalytical; Model: Aeris). A goniometer has used to maintain the angle and rotate the sample. The patterns have recorded with scan parameters target material Cu, voltage 40 kV,current15 mA, angular parameter 2θ 2º to 50º at a step size of 0.022º, length of 2θ3.02, scan time 36s, specimen length10mm, temperature 25ºC, Cu Kαα radiation 1.5418Å, K-β1.392, K-α2/K-α1 0.5.

Characterization

The U.V. spectra of Hydrochlorothiazide have scanned by using a U.V. spectrophotometer (Make: Shimadzu; Model: UV2600). The linearity solutions were prepared individually with the final concentrations of 10 - 25ppm standard solutions in methanol and determined the maximum absorbance in a range of 200-400nm.

Fourier transformed-Infrared (FT-IR) Spectroscopic study of drug coverage in the region of 4000 to 650cm^{-1}has conducted on Bruker Alpha FTIR spectrometer with ATR accessory. Obtained spectra were the average of 16 scans at a resolution of 4cm^{-1}.

The 500 MH$_z$ NMR Spectra studies have carried by using ^{1}H and ^{13}C- Nuclear Magnetic Resonance Spectrometer (Make: JEOL Model: ECZ400S/L1). The tetramethylsilane (TMS) as an internal standard). With the offset 7/100ppm, sweep 18/250ppm, 30-45°C pulse with 16 number of the scan.

The LC-MS analysis and detection for the drug substance have carried out using HPLC (Model: 2689-SQD-2 make: Waters) equipped with electron spray ionization operated in combined mode. The mobile phase used was 5mM ammonium acetate in water and acetonitrile in a ratio of 20:80 in an Isocratic method at a flow rate of 0.2ml/min and

run time was 3min. The desolvation gas flow1000 L/hr, cone gas flow 25L/hr,capillary voltages:3.5 kV,conevoltage: 50 V,desolvation temperature: 350°C.

Thermal properties of the drug substance have analyzed by using a Differential Scanning Calorimeter (Model: Q20; Make: T.A. Instruments). The sample placed on a thematically sealed pan and has heated in a temperature range of 20 to 350°C at 10°C/min temperature ramp, using nitrogen at a flow rate of 50 mL/min for the inert atmosphere.

Assay and Related substance of Hydrochlorothiazide has determined by using UPLC (Model: H-Class) with PDA detector at 254nm. BEH C18; 1.7µm; 2.1mm I.D x 50mm Length UPLC column previously stabilized at 40□C with 0.5mL per minute flow rate has used. 0.1%v/v formic acid in water as a buffer (Mobile phase A) and the mixture of methanol/acetonitrile in a ratio of 10:90 v/v (mobile phase B) with gradient ratios95/5 up to 0.5min/ 3-4min, 70/30 at 1.2 min, 50/50 at 2min with 0.5mL per minute flow rate and 1.0µL injection volume. The standard and sample solutions have been prepared with a concentration of 25µg/mL of Hydrochlorothiazide in Methanol. The quantification of impurities A, B and C has identified and calculated by % content per dosage unit.

Compatibility Studies:

To evaluate the impact of excipients on physical and chemical stability, dissolution, and ultimately bioavailability of the drug formulation. The Drug and excipients namely corn starch, MCC (Avicel PH 101); Crospovidone; PVP K-30, magnesium stearate, croscarmellose sodium, DCP and SSG blend in 1:1 ratio according to dose proportionate was mixed and filled in type-I glass vials (open vials & vials sealed with rubber stopper) and has stored in the Stability chamber (Model: TH 400 S/G; Make: Thermo lab) at 40ºC + 2 ºC / 75% R.H for one month.

RESULTS AND DISCUSSION

Solubility studies for saturated solutions of the API (HTZ) have carried out over the pH range of 1.2-6.8. The data of the solubility studies have shown in table 1. The solubility of Hydrochlorothiazide in the water at 37°C is 430.5mg/L. Further, the solubility is not affected significantly ($P \leq 0.05$) in the buffer solutions in a pH range of 1.2 to 6.8. The solubility graph has shown in figure 2.(Table 1)

Table 1: Solubility data of Hydrochlorothiazide

Sr. No	Name of Solubility Media	Mean Solubility (mg/L), n=3
1	Water	430.5± 1.8
2	0.1N HCl, pH 1.2	440.4± 1.1
3	0.1NHCl, pH 1.2 + 1% SLS	430.3± 1.9
4	Acetate buffer, pH 3.0	430.9± 1.3
5	Acetate buffer, pH 4.0	422.3± 1.2
6	Phosphate buffer, pH 5.0	435.4± 0.8
7	Phosphate buffer, pH 6.8	432.2± 1.6
8	0.1N Sodium hydroxide	434.7± 1.8

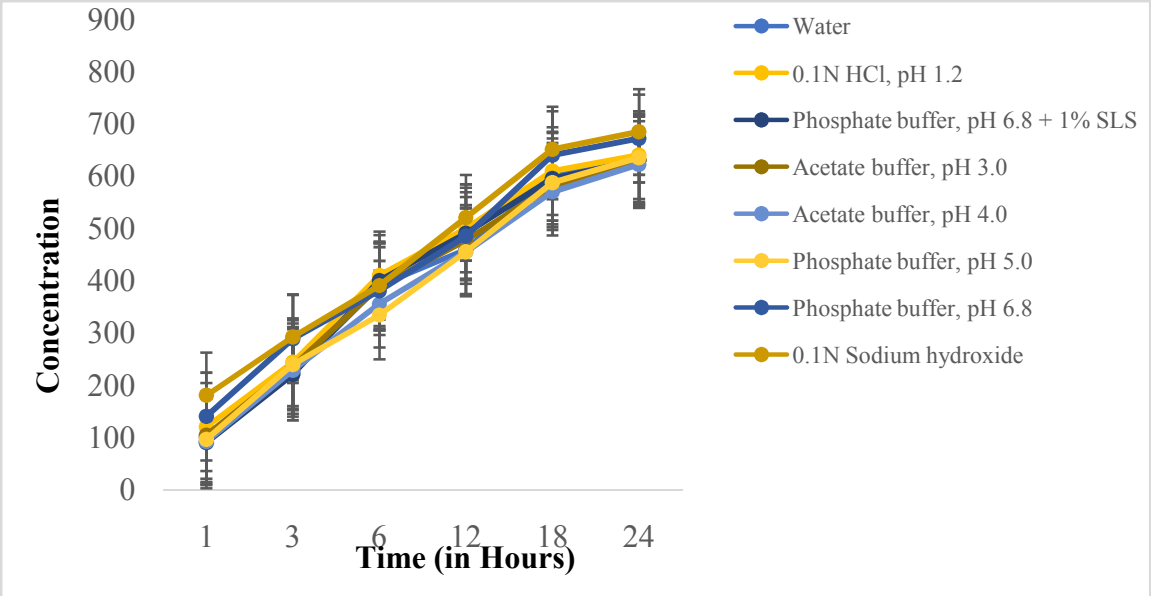

Figure 2: Typical Solubility graph of Hydrochlorothiazide

Particle size distribution study

The PSD histogram has represented in figure 3, conforms, the presence of DV (10) 3.13 µm; Dv (50) 15.8 µm; Dv (90) 98.1 µm and Dv (95) 151 µm particles in the crystalline material. (Figure 3)

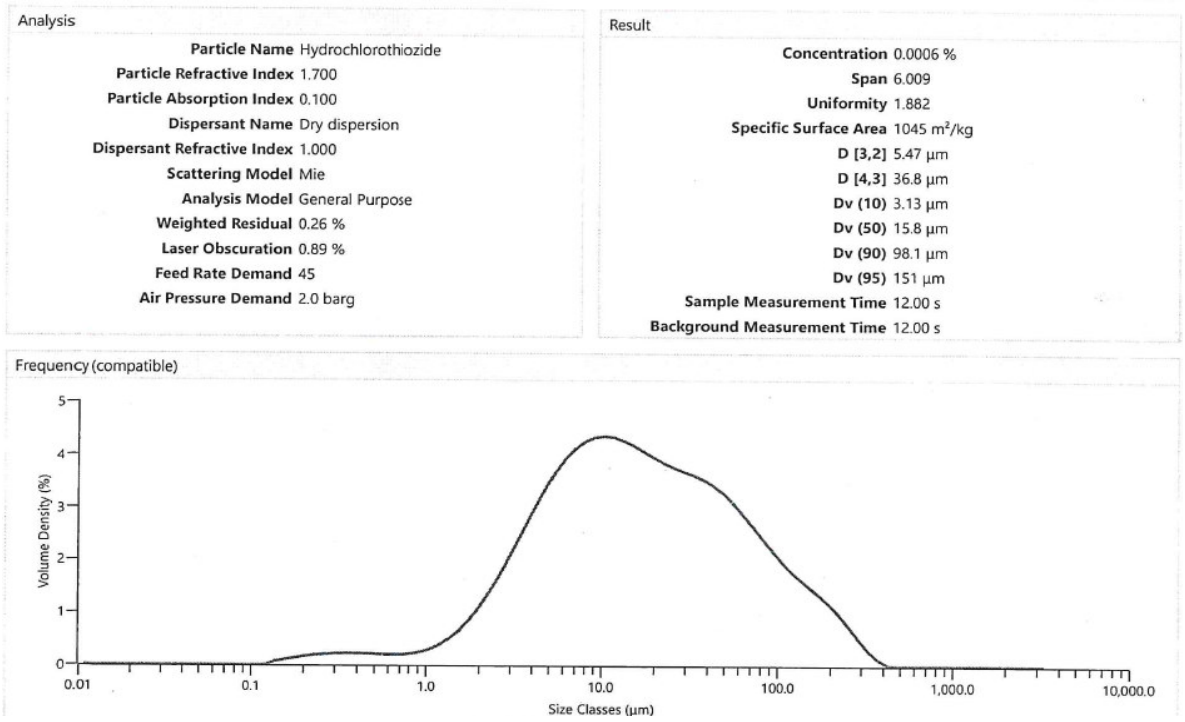

Figure 3: Typical PSD Histogram of Hydrochlorothiazide

X-ray diffraction

The main characteristics of diffraction line profiles are 2θ position, peak height, peak area, and shape from figure 4, and the diffraction line profiles 2θ values are at 9.4979°, 19.0697°, 20.8479°, 20.4798°, 21.3794°confirms to form A solid phase. (Figure 4)

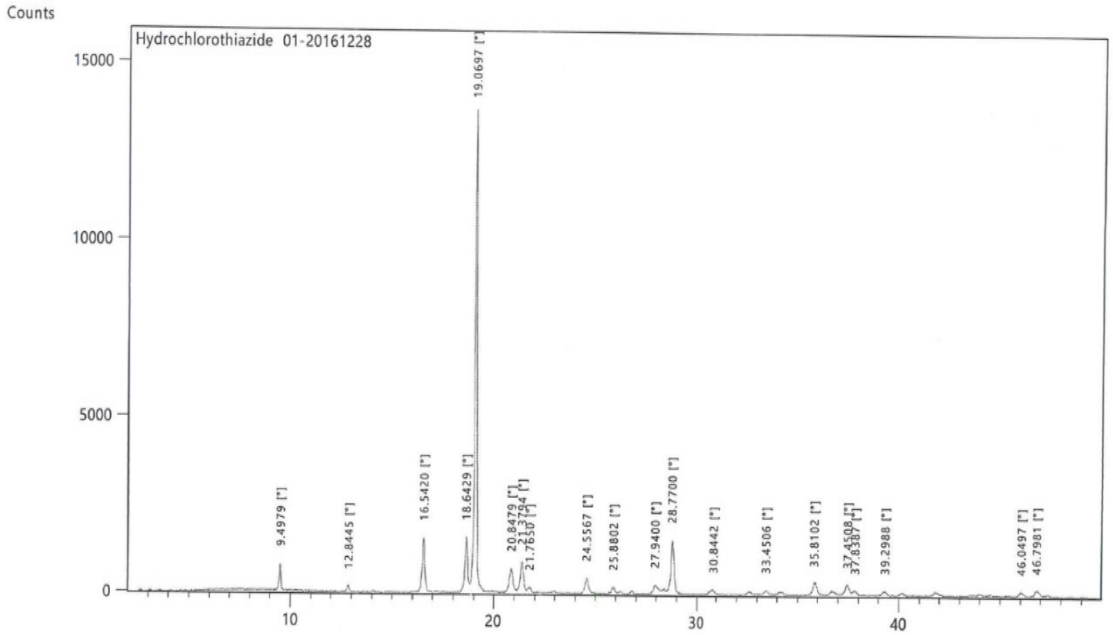

Figure 4: Pattern of X- ray Diffraction of Hydrochlorothiazide

Characterization Studies

UV-Visible Spectroscopy

The U.V. spectrum of the pure drug (API)has scanned by using Shimadzu Model: UV-2600 instrument in a range of 200nm to 400nm. The drug Standard solution exhibits the characteristic 3 maximum absorbances at 317nm, 270nm and 225nm. For quantification 317nm have selected and it is in the linear range of absorbance from figure 5.

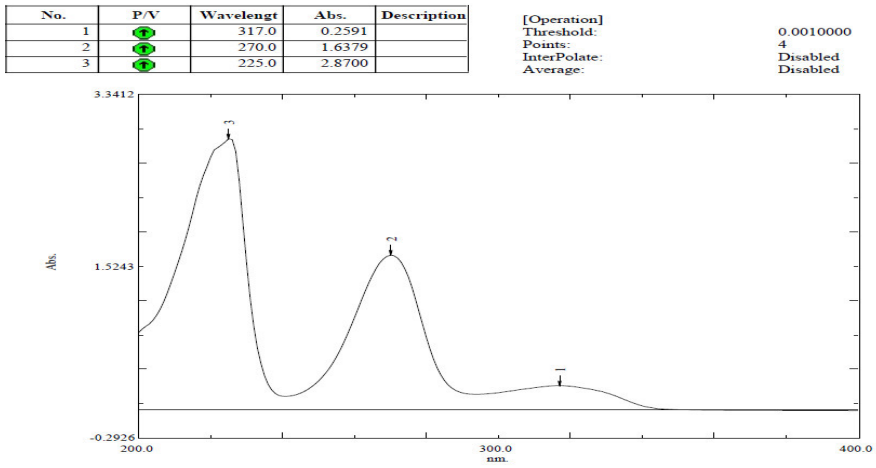

Figure 5: Typical UV Spectrum of Hydrochlorothiazide

Fourier transformed infrared spectroscopy

The FT-IR spectrum of pure Hydrochlorothiazide from figure 6, reveals the characteristic peaks, which included broad absorption bands at 3362cm^{-1}, 3267cm^{-1}for hetero aromatic- N-Hstretching (Thiadiazide) and 3170cm^{-1} for the NH-stretching in amine (SO2 NH2), the absorption peaks at 1335cm^{-1} for SO2 asymmetric stretching and 1181 cm^{-1} and 1151 cm^{-1} for the SO2 symmetric stretching vibrations. The characteristic peaks at 2947cm^{-1} and 2835cm^{-1}for CH_2 stretching, at 1604cm^{-1}, 1521 cm^{-1} for C=C stretching, at 907 cm-1for S-N stretching vibrations, and absorption at1243cm-11274 cm^{-1}for C-N stretching (1,2,4-Thiadiazide ring). (Figure 6)

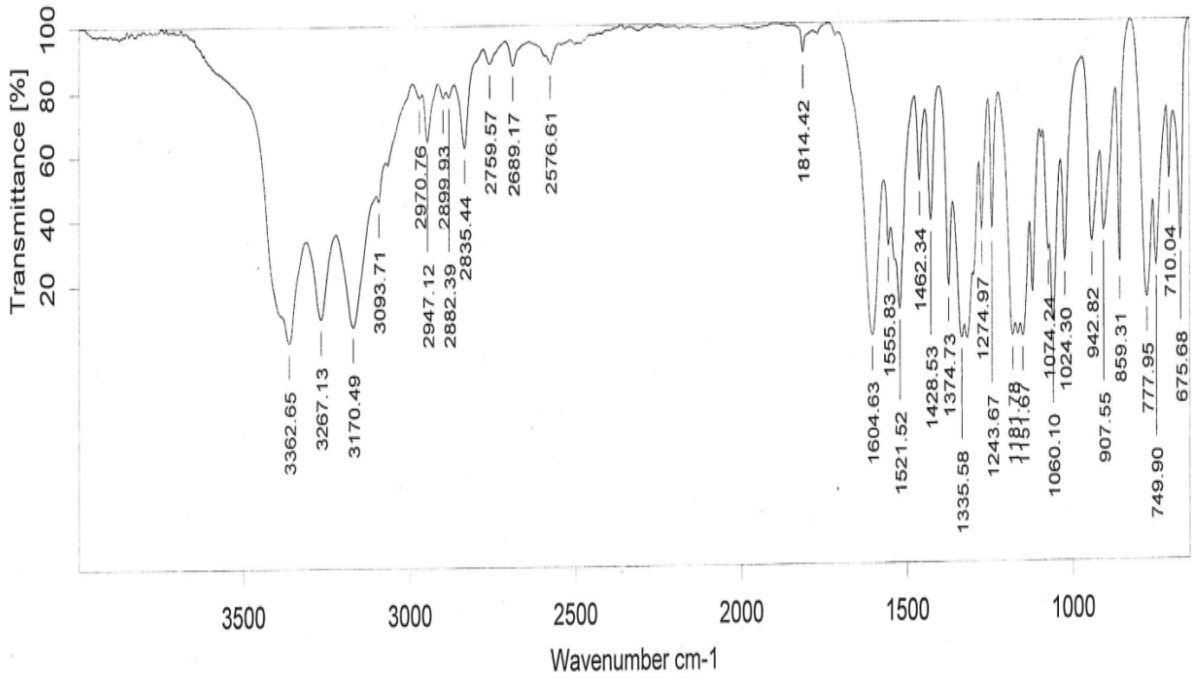

Figure 6: Typical FTIR spectrum of Hydrochlorothiazide

Nuclear magnetic resonance spectroscopy

^{1}H NMR spectrum from figure 7, shows signals at 7.95 (1H, t, J=8.1Hz), and 8.01 (1H, s) corresponding to -NH protons at N-2 and N-4 of thiadiazine. The spectra further reveal two singlets at 6.97(1H, s) and 7.99 (1H, s) each of one proton present at C-5, and C-8, and a multiplet at 4.72(2H, m) ascribed to protons at C-3 of benzo thiadiazine. The spectrum also displays a singlet at 7.49(2H, s) attributed to the sulfonamide group at C–7 of benzo thiadiazine. The ^{13}C NMR spectrum from figure 8 shows signals at 125.6, and 146.6ppm assigned to C-10 and C-9 carbon atoms of ring fused from the structure. The signals at 54.4; 117.1ppm; 118.5ppm; 127.9ppm; 134.4ppm assigned to C-3 (-CH_2), C-5 (-CH), C-7 (-C-), C-8(-CH), and C-6 (-C-) carbon atoms of the compound. The carbon skeleton conforms to Hydrochlorothiazide. (Figure 7, 8)

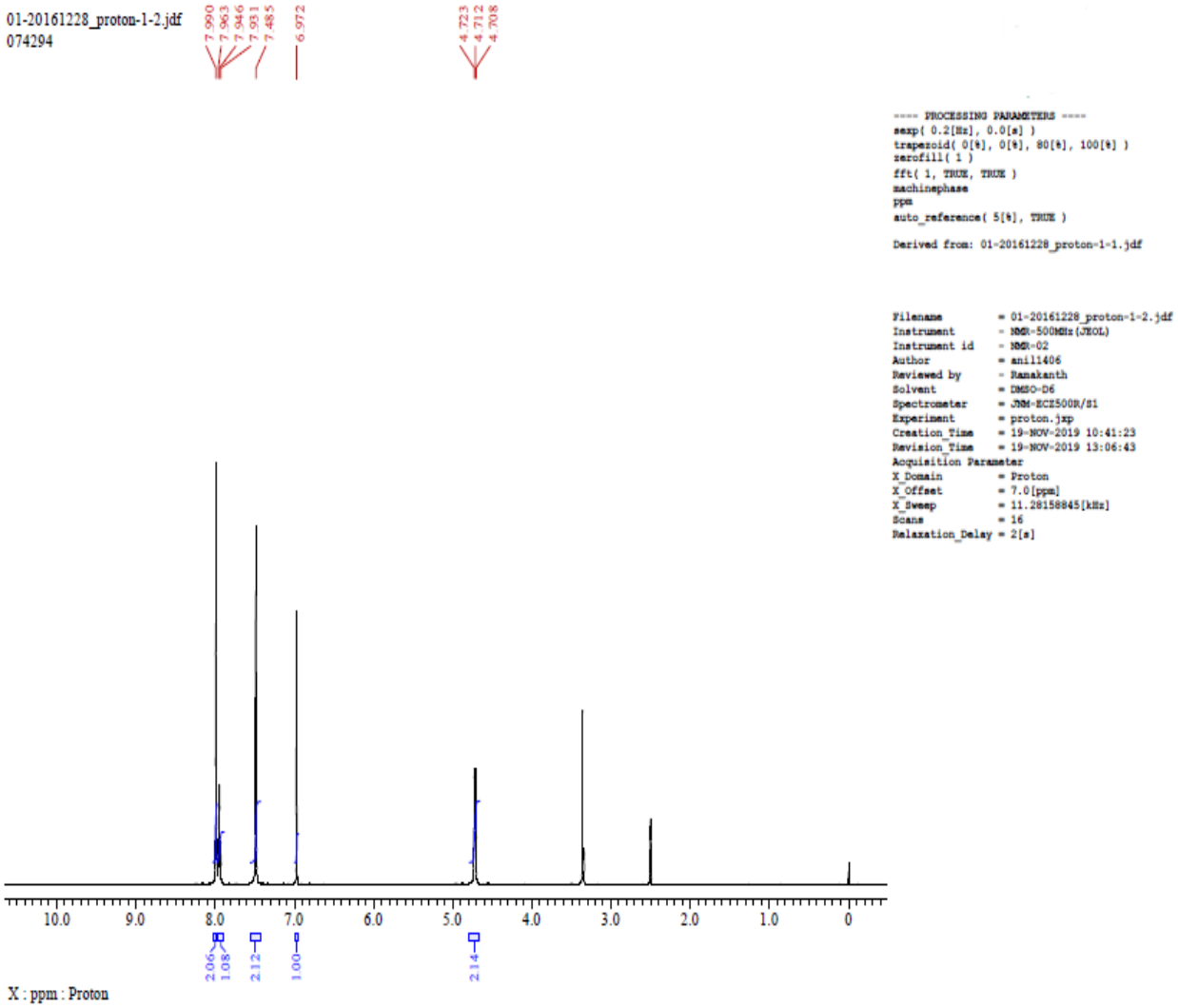

Figure 7: 1H NMR Spectrum of Hydrochlorothiazide

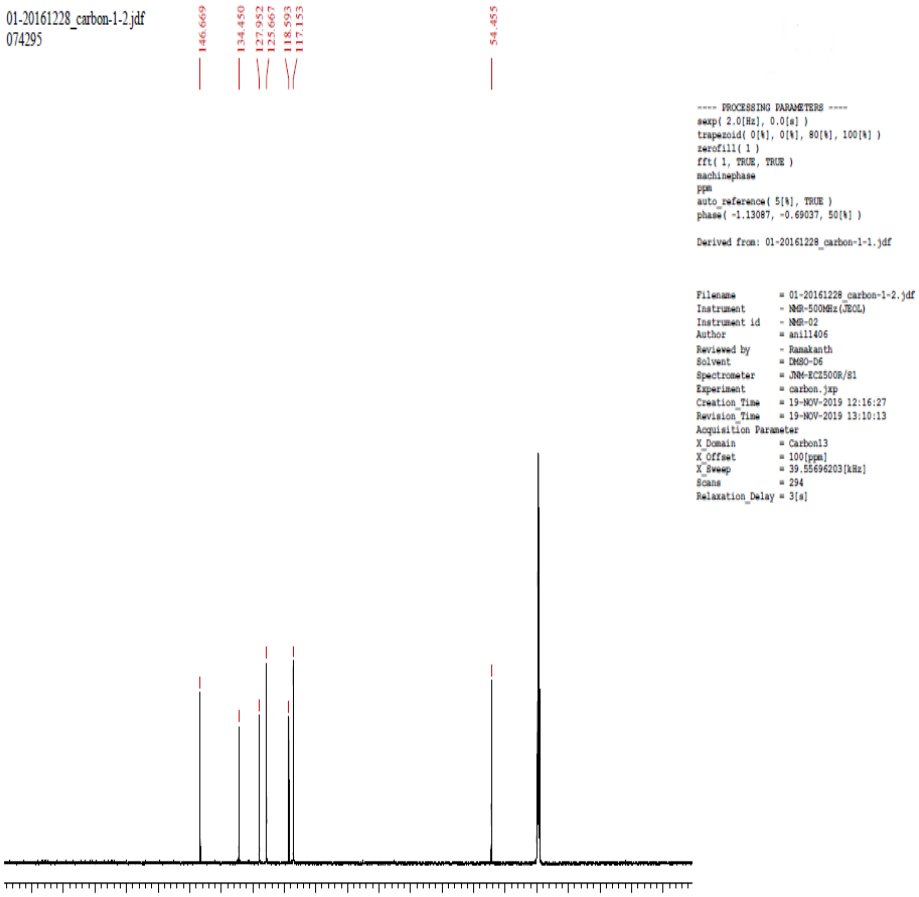

Figure 8: 13C NMR Spectrum of Hydrochlorothiazide

Mass Spectrometry

The molecular ion provides the molecular mass of the analyte. The molecular ion mass for API has predicted in E.S. combined mode. A molecular ion (M-1)– was recognized at m/z 296.0 in negative ion mode, which confirmed that the molecular weight of Hydrochlorothiazide is 297.741g per mol. Themass spectrum has shown in figure 9.

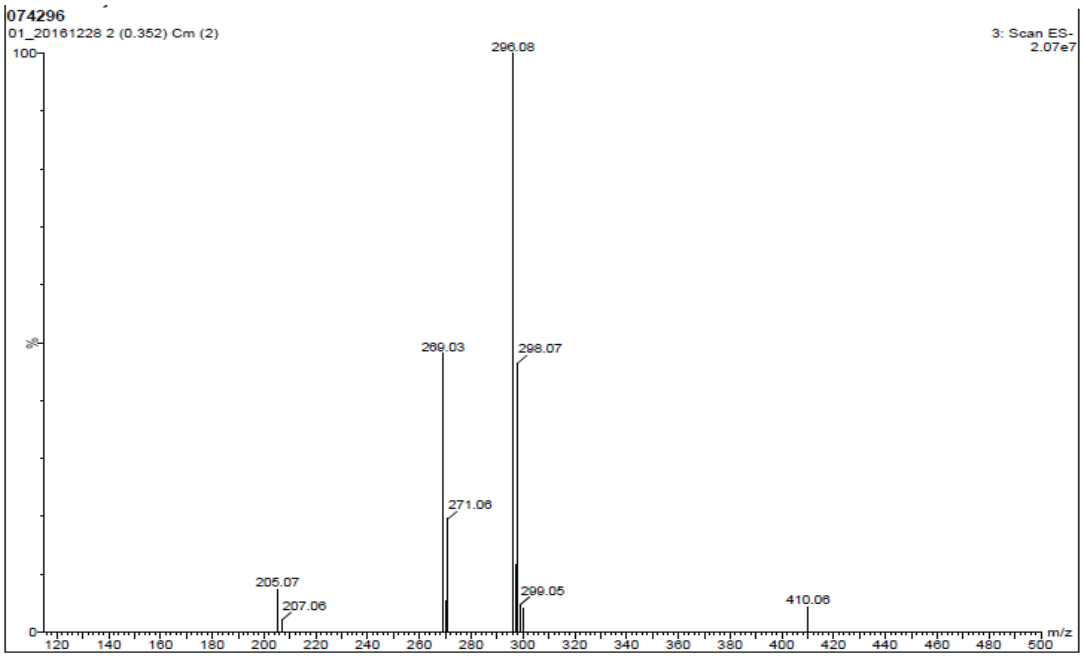

Figure 9: Typical Mass spectrum of Hydrochlorothiazide

Differential scanning Calorimeter

The differential scanning calorimeter (DSC) is a fundamental tool in thermal analysis. Melting is an endothermic process that requires the absorption of heat. The temperature remains constant during melting despite continued heating from 20 to 350°C with a rate of 10°C/min. From the DSC thermo gram representing in figure 10, the peak has observed at 268.96°C, and the onset value is 265.64°C represents the characteristic endothermic peak of Hydrochlorothiazide. The energy required for melting is 138.5J/g. (Figure 10)

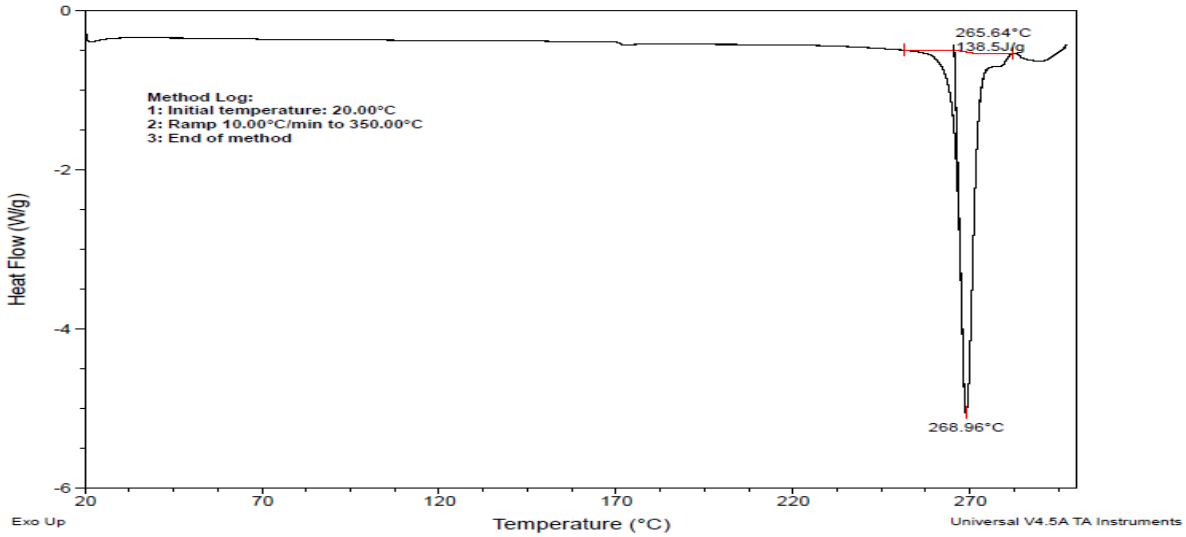

Figure 10: Typical DSC graph of Hydrochlorothiazide

Drug-Excipients Compatibility studies

To obtain the desired drug product tablet excipients with appropriate functions were evaluated. The FT-IR spectra of Hydrochlorothiazide and excipients have overlaid to identify probable chemical interaction between them. The Corn starch exhibits broadband around at 3300cm^{-1}(-OH group), the stretching vibrations at 1082cm^{-1}(C-O bond of the C-O-C group) in the anhydrous glucose. In the case of magnesium stearate, the spectrum shows a stretching vibration in the region of 2917cm^{-1} to 2850cm^{-1}(CH2-CH3), asymmetric stretching vibrations at 1577 cm^{-1}, and 1466cm^{-1} (COO- group). In respect of microcrystalline cellulose spectrum, broadband at 3383cm^{-1} and band at 1635 cm^{-1} are due to starching, and bending vibrations of a -OH group, asymmetric stretching vibration of C-H in the pyranoid ring has appeared at 2900cm^{-1}and C-H bending vibration at 1338 cm^{-1}. The broad absorption peak at 1059cm^{-1}(C-O stretching in C-O-C) of cellulose. The FT-IR spectrum of PVP K30 and Crospovidone showed similar characteristic absorption bands as follows. An absorption peak at 1654cm^{-1} and 1645 cm^{-1}(-C=O group). Broadband at 3426 cm^{-1}, and 3443 cm^{-1}(-OH).Stretching vibrations of absorbed water, indicating hygroscopic nature. The Characteristic peaks at 2,958 cm^{-1} and 2957cm^{-1}(C–H stretching), and 1424 cm^{-1}(N–H). The sodium starch glycollate, Croscarmellose sodium FT-IR spectra showed identical characteristic bands such as C=O stretching at 1598cm^{-1}, and 1634cm^{-1}, -OH stretching vibration at 3441cm^{-1}, and 3443cm^{-1}. The absorption bands of component shave been observed that the FT-IR spectrum of API (HTZ) showed a superposition of peaks from the excipients, indicated that there were no intermolecular interactions between them (figure 11).

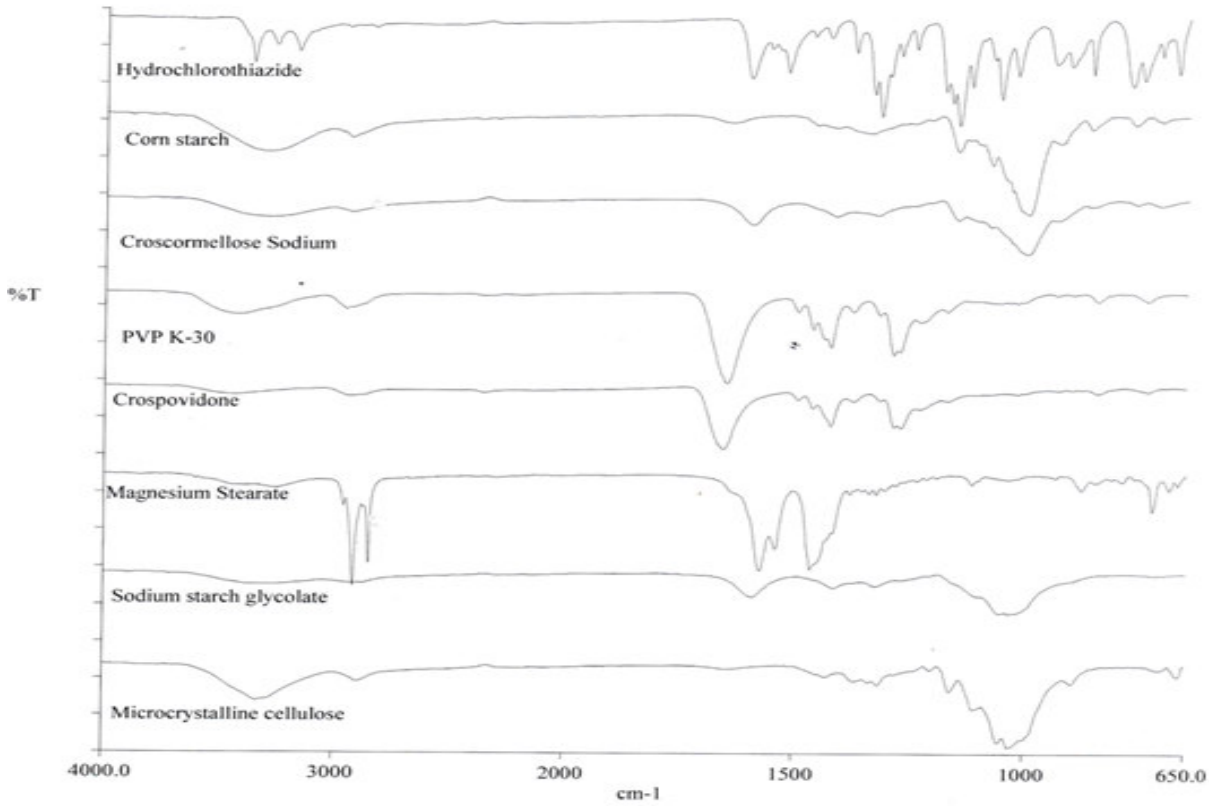

Figure 11: Overlay FTIR Spectra of Hydrochlorothiazide and excipients

DSC studies furnish about the physical nature of the sample as crystalline or amorphous and reveal a probable physicochemical interaction between drugs and polymers in formulations. The thermal profile of Hydrochlorothiazide discloses a melting point of 273ºC, the endothermic peak observed for the drug is at 268.96ºC. While the drug melting peak is quite visible in the physical mixture of Hydrochlorothiazide, and MCC (1:1) thermo gram at 268.75ºC, Therefore the thermo grams of the material mixture showed that no interaction between Hydrochlorothiazide and MCC. The thermo grams of pure Hydrochlorothiazide and Hydrochlorothiazide and MCC mixture have shown in figure 12.

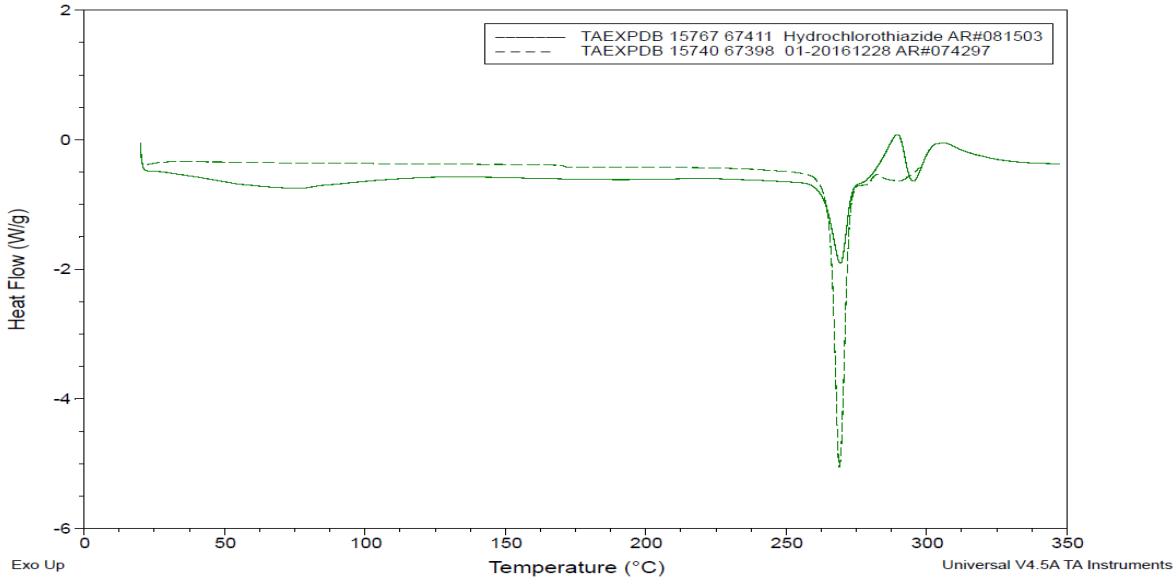

Figure 12: Overlay thermo gram of Hydrochlorothiazide and Hydrochlorothiazide blend with excipients mixture.

The Assay result from Table 2 for Hydrochlorothiazide is greater than 99%, and the relative standard deviation is <1.0% from the initial results to 30th-day results. The calculated confidence interval at 95% level from descriptive statistics is 0.21 represents no significant change in the assay results from the initial. The related impurities Chlorothiazide (impurity A) are varied from 0.11% to 0.29%; Salamide (impurity B) is varied 0.13% to 0.28%; Hydrochlorothiazide

Dimer (impurity C) is varied from 0.11% to 0.29% from entire study intervals. (Table 2)

Table 2: Compatibility results of Hydrochlorothiazide API and Hydrochlorothiazide with Excipients Mixture

Mixture Name	Condition 40°C/75%RH (1M)	Assay (%)	% Impurities			
			A (%)	B (%)	C (%)	Any other impurity (%)
Hydrochlorothiazide API	Initial (0 Hour)	99.8±0.5	0.15±0.001	0.13±0.001	0.11±0.005	BDL
	7th Day	99.6±0.2	0.16±0.005	0.15±0.005	0.14±0.003	BDL
	15th Day	99.3±0.7	0.22±0.002	0.21±0.001	0.19±0.002	BDL
	30th Day	99.2±0.5	0.26±0.002	0.25±0.001	0.23±0.001	BDL
Hydrochlorothiazide + Corn starch	Initial (0 Hour)	99.7±0.9	0.11±0.001	0.14±0.002	0.15±0.001	BDL
	7th Day	99.6±1.1	0.17±0.003	0.17±0.003	0.17±0.002	BDL
	15th Day	99.4±1.5	0.21±0.002	0.22±0.003	0.21±0.003	BDL
	30th Day	99.3±0.3	0.24±0.006	0.27±0.001	0.24±0.002	BDL
Hydrochlorothiazide + Avicel PH 101	Initial (0 Hour)	99.6±0.4	0.14±0.008	0.13±0.003	0.12±0.005	BDL
	7th Day	99.5±0.8	0.19±0.002	0.18±0.005	0.13±0.003	BDL
	15th Day	99.3±1.2	0.23±0.003	0.24±0.004	0.17±0.002	BDL
	30th Day	99.1±0.9	0.26±0.005	0.26±0.004	0.23±0.001	BDL
Hydrochlorothiazide + Crospovidone	Initial (0 Hour)	99.5±1.1	0.11±0.002	0.14±0.006	0.13±0.002	BDL
	7th Day	99.4±0.8	0.22±0.001	0.21±0.007	0.19±0.003	BDL
	15th Day	99.2±0.9	0.24±0.003	0.24±0.006	0.23±0.004	BDL
	30th Day	99.0±0.9	0.27±0.001	0.29±0.006	0.27±0.001	BDL
Hydrochlorothiazide + PVP K-30	Initial (0 Hour)	99.4±1.2	0.14±0.002	0.12±0.005	0.11±0.002	BDL
	7th Day	99.3±1.1	0.19±0.002	0.18±0.003	0.16±0.003	BDL
	15th Day	99.1±1.4	0.26±0.001	0.23±0.002	0.21±0.002	BDL
	30th Day	99.0±1.3	0.29±0.001	0.27±0.001	0.26±0.001	BDL
Hydrochlorothiazide + Sodium starch glycolate	Initial (0 Hour)	99.4±1.2	0.14±0.004	0.12±0.003	0.11±0.002	BDL
	7th Day	99.3±1.5	0.19±0.002	0.18±0.004	0.16±0.003	BDL
	15th Day	99.1±0.9	0.26±0.003	0.23±0.006	0.21±0.004	BDL
	30th Day	99.0±0.7	0.29±0.004	0.27±0.004	0.26±0.003	BDL
Hydrochlorothiazide + Magnesium stearate	Initial (0 Hour)	99.6±0.3	0.11±0.007	0.13±0.002	0.12±0.002	BDL
	7th Day	99.4±0.8	0.15±0.006	0.16±0.001	0.14±0.002	BDL
	15th Day	99.3±0.8	0.21±0.005	0.21±0.003	0.19±0.003	BDL
	30th Day	99.2±0.2	0.26±0.004	0.24±0.001	0.23±0.004	BDL
Hydrochlorothiazide + Crosscormellose sodium	Initial (0 Hour)	99.5±1.1	0.15±0.002	0.12±0.002	0.13±0.003	BDL
	7th Day	99.4±1.0	0.18±0.003	0.17±0.003	0.16±0.005	BDL
	15th Day	99.2±0.7	0.24±0.004	0.22±0.004	0.23±0.004	BDL
	30th Day	99.1±0.6	0.28±0.002	0.26±0.002	0.29±0.005	BDL
Hydrochlorothiazide + Dibasic calcium phosphate	Initial (0 Hour)	99.4±0.9	0.16±0.003	0.17±0.002	0.12±0.003	BDL
	7th Day	99.2±0.9	0.14±0.004	0.19±0.001	0.17±0.003	BDL
	15th Day	99.1±1.2	0.25±0.002	0.25±0.003	0.24±0.004	BDL
	30th Day	99.0±1.1	0.27±0.002	0.28±0.002	0.28±0.001	BDL

CONCLUSION

Pre formulation studies give directions for the design of formulation in choice of drug form, excipients, and composition. The PSD Histogram of Hydrochlorothiazide indicated that it is a crystalline powder. The FT-IR overlay spectra have indicated no intermolecular interactions between Hydrochlorothiazide and excipients. In the DSC thermo grams of a physical mixture, and the DSC graph of Hydrochlorothiazide, the drug melting peak was quite visible proves that no physiochemical interaction between Hydrochlorothiazide and excipients. Therefore, the selected excipients were compatible with Hydrochlorothiazide and

employed to assist in the preparation of Immediate-release granules of this therapeutic agent and further development of anti-hypertensive bilayer tablets.

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ETHICAL CLEARANCE

The research work has not carried on any animal or human, and work has carried on chemical and instrumental analysis.

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CONFLICT OF INTEREST

The S.M. Pharmaceuticals SdnBhd, Research and Development Centre had no association in the writing of the manuscript as well as in the decision to submit the article for publication. The authors have indicated that they have no competing interest regarding the content of this article.

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