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Original Article

Formulation and Evaluation of Nanocrystals of Hydrochlorothiazide

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ABSTRACT

Aim/Background: Hydrochlorothiazide (HTZ) is a diuretic derivative and used as an antihypertensive agent with low bioavailability (around 60%) due to impaired dissolution rate. Further, excretion of HTZ is high due to rapid renal clearance (~ 320 mL/min). **Objectives:** Aim of the current study to improve dissolution rate of HTZs through nanocrystals technology. **Materials and Methods:** Nanocrystals (NC) were prepared by controlled precipitation method varying two different approaches. From the first aspect NC were prepared without stabilizer, and from the second aspect NC were prepared using different stabilizer. NC formulations were physically characterized, *in vitro* dissolution rate and assessment of storage stability. **Results:** Physical characterization of HTZ NC using FTIR, DSC, and SEM revealed no changes took place in the drug quality attributes. The particle size, zeta-potential, and PDI measurement of NC exhibited their nano-size range in 252 nm, -15.5 mV, and 0.230 respectively. Dissolution rate of NCs were significantly improved in comparison to pure drug. The optimized batch AF2 was stable at room temperature (25±0.5ºC) and elevated temperature (40±1ºC) with 75±5% RH over the period of 60 days. However, drug assay of AF2 showed a slight decrease over the time at room temperature (25±0.5ºC), while degradation rate was enhanced at the elevated temperature (40±1ºC) with 75±5% RH. Based on physical characterization, *in vitro* release and stability studies, it can be concluded that NCs of HTZ (AF2) was stable for an extended period of time and provides improved dissolution rate. **Conclusion:** Nanocrystals of hydrochlorothiazide were successfully formulated by using different stabilizer which leads to the enhancement of dissolution rate and storage stability.

Keywords: Hydrochlorothiazide, Mannitol, Nanocrystal, Dissolution rate, Solubility, Storage stability.

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INTRODUCTION

Nanotechnology has a profound and transformative impact on various aspects of our lives, spanning technology, medicine, and pharmacy.[1] Its influence is pervasive, manifesting in the production of computer chips, the burgeoning field of biotechnology, and even in cosmetics, where nanoscale agents offer a wide array of benefits. Across these domains, the pursuit of smaller size is a common thread, driving continuous improvement and diverse applications. In the realm of medicine and pharmaceutics, nanotechnology plays a crucial role in enhancing human health at a molecular level. Exciting and promising applications include the development of diagnostic tools, the formulation of drug carrier systems, and advancements in gene therapy. By manipulating materials to the nanoscale, their physical properties undergo profound changes, enabling the development of innovative formulation principles for poorly soluble drugs in the field of pharmaceutics.[2,3] The ideal drug should possess certain properties such as enhanced solubility and dissolution, improved bioavailability and absorption, the ability to eliminate food effects, safe dose escalation, enhanced safety, and desirable efficacy and tolerability profiles. Nanoparticles, with their unique size and surface features, exhibit these remarkable advantages. When materials are reduced to the nanoscale, their physical properties undergo significant changes.[4] This concept has paved the way for novel inventions in the field of pharmaceutics, opening up new possibilities for drug formulation and delivery systems. Nanoparticles have the potential to revolutionize the pharmaceutical industry by addressing the challenges associated with poorly soluble drugs and offering improved therapeutic outcomes.[5,6]

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In drug therapy, solubility is indeed a critical factor in pharmaceutical development, as it directly impacts the bioavailability and effectiveness of a drug. However, it presents a significant challenge for developing new pharmaceutical products, around 40-70% of newly discovered active pharmaceutical ingredients (APIs) have poor water solubility, resulting in low oral bioavailability, leading to challenges in achieving optimal bioavailability. This low solubility often necessitates innovative formulation strategies to improve the dissolution and absorption of these drugs, ensuring their therapeutic effectiveness.

MATERIALS AND METHODS

Materials

Hydrochlorothiazide was gift sample obtained from M/s Yes Pharma Pvt. Ltd., Roorkee, Uttrakhand (India). All other materials used were of pharmacopeial grade. The details description of drug (HTZs) are 6-chloro-3, 4-dihydro-2, 2,4-benzothiadiazine-7-sulfonamide 1, 1-dioxide (chemical name), $C_7H_8ClN_3O_4S$ (empirical formula), molecular weight 297.72, physical form is white, fluffy, microcrystalline powder, soluble in dilute NH_3, NaOH, CH_3OH and C_3H_6O, melting point 273-275°C and biological half-life 5.6-14.8 hr.[7-8] And the description of excipient (Mannitol) are D-Mannitol (IUPAC name), $C_6H_{14}0_6$ (molecular formula), 182.17 (molecular weight), appearance was white, odourless, crystalline powder, melting point b/w 166-168°C and solubility, ethanol-1 in 83 and water-1 in 5.5 at 20°C. Another description of excipient (Isopropyl alcohol) was Isopropanol or N-propanol (IUPAC name) C_3H_8O (molecular formula), 60.09 (molecular weight), physical characterization of IPA that was clear, colorless liquid, very flammable with high vapor pressure, miscible in water, alcohols, ether and chloroform, insoluble in salt solutions (NaCl).[9-10]

Methods

Method of Preparation

Nanocrystal was prepared by precipitation method.[11] This method is employed from two different aspects.[12] From the first aspect nanocrystals was prepared without stabilizer and from the second aspect nanocrystals was prepared using different stabilizer.[13-17]

Nanocrystal without Stabilizer

In this aspect, nanocrystals are prepared by anti-solvent precipitation method. In this method, poorly water-soluble drug was dissolved in a solvent (an organic solvent in which drug is miscible), and resulting solution is added into an aqueous solvent under continuous agitation with constant temperature. This results in rapid high super saturation, leading to rapid nucleation and precipitation.[18]

Preparation of Nano Suspension

Two separate solutions were prepared: Hydrochlorothiazide in isopropyl alcohol (drug solution); mannitol in water (aqueous solution), maintained both solutions at 60°C. The aqueous solution was mixed with IPA solution while maintaining at 60°C. After mixing, transparent mixture is obtained. The resulting mixture is kept in vacuum desiccator to obtain a sponge or rubber like structure.[19]

Lyophilization of Nano Suspension

Dry the formulation with the help of lyophillizer to obtain Nanocrystals. Prepared semisolid formulations were kept frozen using deep freezer at -20°C for 24 hr before lyophilization. Obtained formulations were freeze dried with the help of lyophillizer for 36 hr to completely dry. All the formulation of nanocrystals of Hydrochlorothiazide from batch code AF1to AF5 is shown in the Table 1.

Evaluation Studies

Differential Scanning Calorimetry

DSC was performed to determine the heat of fusion of HTZ and mannitol in nanocrystals. Thermal analysis, including melting point and enthalpy measurements, were used for this purpose. DSC is a technique used to measure the heat flow associated with physical and chemical changes in the materials as a function of temperature.[20-21]

For the analysis, approximately 2-4 mg of each sample was weighed and placed into aluminum crucibles. The crucibles were then sealed using a sealing machine with aluminum lids. The thermograms were obtained by heating samples at a rate of 10°C/min in temperature range of 10-350°C, under an inert nitrogen atmosphere. The enthalpy difference between melting peak and crystallization peak of a sample, compared to melting peak enthalpy of the unmodified drug, is a common method to assess the degree of crystallinity in solid dispersions.[22]

By observing the variation in heat of samples with respect to temperature changes, important information about crystallinity, thermal behavior of HTZ and mannitol in the crystallized dispersions can be obtained.[23]

Analytical State Depiction

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of pure drug HTZ, mannitol and nanocrystal were determined by using FTIR spectrometer model Shimadzu 8400S. Each sample (5mg) was mixed with potassium bromide (100mg) to form pellet and their spectra were recorded in range of 400-4000cm^{-1}.

Photon Correlation Spectroscopy (PCS)

PCS were employed to ascertain z average and polydispersity index by using zetasizer. The z-average is a measure of mean size of particles in a sample, weighted by their intensity. It represents size of particles in the bulk population. The z-average diameter is calculated based on fluctuations in the intensity of scattered light caused by Brownian motion of particles in the sample. Polydispersity index (PDI) measures the width of particle size distribution in a sample. It is calculated as ratio of standard deviation of particle size distribution to the mean particle size (z-average diameter). For monodisperse particle population the PDI value is 0.0, for narrow distribution of particle PDI value should be in range of around 0.10-0.20, however as PDI value increases i.e. 0.5 and above, it shows very broad distribution. To prepare the sample, around 1 mg of prepared nanocrystals is dispersed in 4 mL of dematerialized water hereafter at an angle of 173°C prepared sample were scattered by helium neon laser at constant temperature 25°C. The samples were explored by ten consecutive runs to determine z average diameter and PDI.

Zeta Potential Measurement/ PALS Technique

The zeta potential of all the samples was measured using a Malvern zetasizer equipped with a zeta potential analyzer. The measurements were carried out in distilled water with a conductivity of 50µS/cm and a pH range of 5.5-6, at 25°C. The zeta potential measurement was based on the principle of phase analysis light scattering (M3-PALS) technique, which involves determining the electrophoretic mobility of particles in a thermostatic chamber. This technique allows assessment of zeta potential, indicating the surface charge in samples, and their nanocrystals stability.[24]

Scanning Electron Microscopy

Surface morphology of the samples was analyzed using a scanning electron microscope (SEM) instrumentation model JSM-6490LV JEOL Japan. Nanocrystal samples were evenly distributed on the upper side of a double-sided conductive carbon tape, placed on metal discs coated with a layer of gold/palladium measuring 80nm in thickness. The surface morphology of samples was examined at magnifications of 500x, 1000x, and 2000x. The SEM imaging technique provides valuable insights into the surface characteristics, topography, and morphology of the nanocrystals.

Solubility Screening

The solubility of HTZ was evaluated with the help of orbital shaking incubator. For determination of solubility, the saturated solution of NCs and API (active pharmaceutical ingredient) were taken in different medium i.e. distilled water, phosphate buffer pH 7.2, pH 6.8, and 0.1 N HCl buffer. Samples were constantly shaken unto 48 hr at 37°C±0.5°C in a water bath. The aliquots were withdrawn, centrifuged at 10,000 rpm for 15 min and analyzed for drug content using UV spectrophotometer (Labtronics LT). Each sample was measured for triplicate.

Storage Stability

To assess the long term-stability of nanocrystals, International Conference on Harmonization (ICH) Q1A guideline were followed. Conferring to guideline, the optimized formulation was divided into two batches filled in glass vials with rubber stopper in triplicate manner. First batch was kept in deep freezer maintained at 5°C±3°C for period of 3 months, while second batch of vial were stored at room temperature 25±0.5°C with 75±5% RH for same period of time. To confirm drug stability in NCs, sample were withdrawn to measure its particle size, PDI, zeta potential, drug content, in vitro dissolution and solubility studies after every month. Further, to ensure its accelerated stability profile of AF2 (NCs) was at 40°C±1°C with 75±5% RH for same period of time. Henceforth same process was followed determination of stability.

In vitro Dissolution

Dissolution profile was determined according to United State Pharmacopeia (USP) by utilizing paddle apparatus. NCs equivalent to 50 mg of HTZ was filled in hard gelatin capsule transferred to dissolution apparatus containing, about 900mL of 0.1N HCl as dissolution medium maintained at 37°C±0.5°C run at 100±2 rpm. At precise time intervals of 5, 10, 15, 20, and 30 min samples (5mL) were withdrawn, filtered through 0.45µm membrane and replacing with fresh dissolution media. Samples were diluted with buffer and drug content was analyzed 268 nm using spectrophotometerically at 268.0nm. Dissolution tests were performed in triplicate.

Drug Release Kinetics

To analyze the drug release quantitatively from nanocrystals, different mathematical modelings were applied. These models express drug release as depends upon the nature of the dosage form. While some models are derived from theoretical analysis of the process, in many cases, empirical equations have proven to be more suitable due to the absence of a well-established theoretical concept. The kinetic models describe drug dissolution from new dosage forms, with the dissolved amount of drug (Q) being a function of time (t) or QF (t). Various analytical definitions of Qt are commonly used, including zero-order $Q_t=K_0t$, where Q_t is the amount of drug released in time t, k_0 is the release rate constant for zero order expressed in units of concentration/ time, here zero order kinetic y=2.751x +5.555 and coefficient of determination R^2=0.974, first-order $Q_t - Q_0 (1- e^{-k1t})/ Q_0$ is initial amount off drug; K_1 is release constant for first order, in this model y=0.0526x+0.6766 and R^2=0.6452, Higuchi-matrix Q –kH√t, In this equation, *Q* is the cumulative amount of drug released at time *t, kH* is the Higuchi dissolution rate constant, representing the rate of drug release (units: mass/√time), and *t* is the time, for this model y=15.34x-6.872 and R^2=0.956. In

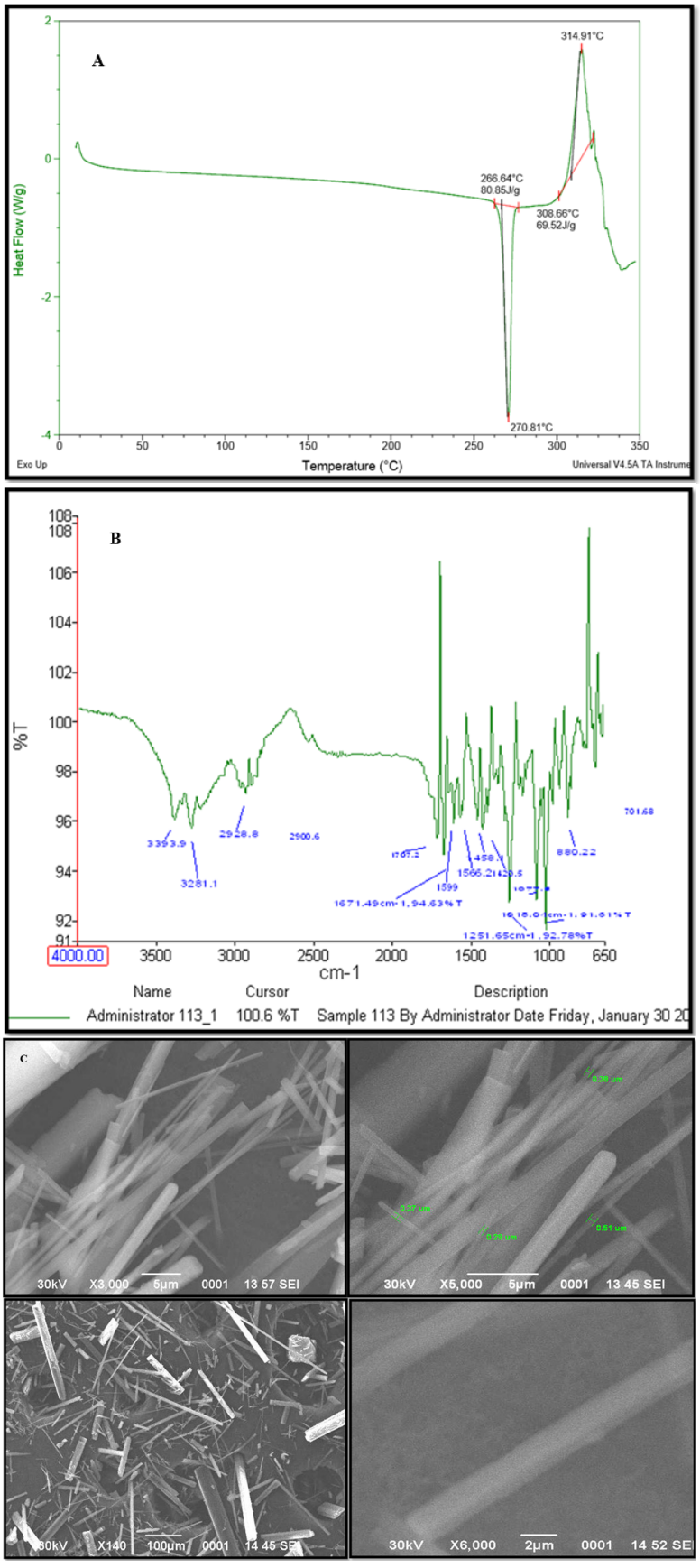

Figure 1: (A) DSC thermogram (B) FTIR and (C) SEM topography of optimized HTZ nanocrystal (AF2) at different magnifications.

the Pappas-Korsmeyer models $Mt/M\infty = k.t^n$, in this equation, Mt is the cumulative amount of drug released at time t, $M\infty$ is total amount of drug in the system, *k* is a constant incorporating structural and geometric characteristics of the system, as well as diffusion coefficient of drug within the matrix and *n* is the release exponent, which characterizes the mechanism of drug release. These models provide a framework for understanding and predicting the drug release behavior, allowing for the evaluation and comparison of different dosage forms.[25-26]

RESULTS

In order to optimize the development of nanocrystal formation, five trial batches (AF1-AF5) were prepared without stabilizer and their compositional detail is given in Table 1. These batches were characterized for particle size analysis, zeta potential measurement, and PDI their data is given in Table 1.

On the basis of desired particle size, PDI, and zeta potential values, trial batch AF2 was selected for further development and process optimization. AF2 demonstrated least nanocrystal size, PDI, and zeta potential, justify its suitability for designing of nanocrystal formulation.

Zeta Potential Analysis

Zeta potential imparts adequate electric repulsion and steric barriers on the surface of nanocrystal, to which restrict their tendency to exhibit particle aggregation. Zeta potential in the range of 0 to ±5 mV shows rapid coagulation and flocculation, while its range in ±10 to ±30 mV shows incipient instability while ±30 to ±40 mV shows moderate stability, ±40 to ±60 mV shows good stability and more than ±61 mV shows excellent stability. The zeta potential of NC formulations is shown in Table 1.

Photon Correlation Spectroscopy (PCS)

The optimized formulation (AF2) has mean particle size of 252 nm. The particle size of NC without stabilizer (AF1, AF3, AF4 and AF5) is found to be 350nm, 323nm, 255nm and 737.6 nm. The PDI is found to be 0.245 for AF1, 0.230 for AF2, 0.252 for AF3, 0.251 for AF4 and 0.493 for AF5. Table 1 shows that particle size of NC formulations.

Differential Scanning Calorimetry

Thermal analysis of pure drug manifests that pure drug absorbs heat with a melting point at 270.81°C with associated enthalpy of fusion 80.85J/g.[27] While the mannitol absorbs heat and has a melting point of 170.35°C. Mannitol has an associated enthalpy of 523.4j/g.[28] The thermal curve of formulation reveals a crystalline state due to associative fusion enthalpy of 287.4j/g-1 having a sharp endothermic effect with 168.70°C. Melting endotherm of nanocrystal system showed that drug is in crystalline form, while amorphous state does not exhibit the melting endotherm. However, sharp peak of the pure drug was disappeared in NC formulation indicates that mannitol as modifier completely shielded the endothermic event of drug. DSC thermograms of nanocrystal formulation are shown in Figure 1A.

Scanning Electron Microscopy

The scanning electron microscopy revealed that NCs exhibit needle like shape with smooth surface. The shape and surface morphology were different for NC formulations. However, needle like structure can be ascribed to mannitol as modifier of surface morphology of pure drug. Scanning electron microscopy of optimized HTZ nanocrystal (AF2) at different magnifications is shown in the Figure 1C.

Solubility Study

The solubility of NC formulations was assessed in different media. The solubility of optimized formulation was found to be 8.20±0.3 mg/mL in distilled water, 6.98±3.2 mg/mL in 6.8 buffer, 6.26±0.5mg/ mL in 7.2 buffer and 8.50±3.2mg/mL in 0.1 N HCl buffer after 24 hr. While the solubility of pure drug is found to be 0.720.3 mg/mL in distilled water, 3.441.2mg/mL in 6.8 buffer, 4.742.5mg/mL in 7.2 buffer and 7.600.8 mg/mL in 0.1 N HCl buffer.

Drug Content

The drug content in formulation was determined by dissolving 10 mg of formulation in 10 mL of methanol. The drug content of all formulation was carried out as par the reported method. Drug content in formulations AF1, AF2, AF3, AF4, AF5, were 92.96±5.8, 95.83±0.6, 94.35±0.82, 96.58±0.92 and 97±2.8 respectively.[29]

Table 1: Formulation of Nanocrystals of Hydrochlorothiazide.

Batch code	C(mannitol/water) (mg/mL)	C(HTZ/IPA) (mg/mL)	Particle size (nm)	PDI	Zeta potential (mV)	Drug loading(%w/w)
AF1	200	50	350	0.234	-12.5	15
AF2	300	50	252	0.230	-15.5	20
AF3	150	50	323	0.252	-12.4	18
AF4	100	50	254.5	0.251	-14.0	25
AF5	50	50	737.6	0.493	5.17	40

Table 2: Release Profile of Nanocrystal without Stabilizer Formulations (Batch code-AF).

Time	AF1	AF2	AF3	AF4	AF5	HTZ
5	39.98±0.05	40.8±1.69	37.22±1.7	45.38±1.2	56.32±0.82	9.03±1.5
10	48.32±2.1	51.32±2.82	46.49±2.4	62.34±0.5	75.92±2.5	28.28±2.2
15	56.3±3.25	60.69±6.3	53.82±2.54	82.5±0.08	90.25±5.2	41.74±4.7
20	80.52±2.12	85.23±4.24	61.32±1.75	95.08±1.52		53.32±4.5
30	87.58±1.86	97.52±0.7	75.54±1.9			63.75±5.6

Dissolution Study

The dissolution study of NCs was performed in 0.1N HCl buffer.[30] The optimized formulation (AF2) shows release of 98% drug in 30 min due to nanosizing meanwhile AF1 and AF3 shows release around 89% and 76% respectively of drug after 30 min. The release of drug in AF4 and AF5 is found to be 95.08% in 20 min and 90.25% in 15 min respectively due to lesser quantity of mannitol. The dissolution profile of nanocrystals formulations without stabilizer (Batch code-AF) and pure drug (HTZ) is shown in Table 2.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of pure drug (HTZ), mannitol and prepared nanocrystals were performed by using FTIR spectrometer model Shimadzu 8400S. The FTIR graph of HTZ nanocrystal formulation was recorded that is shown in Figure 1B.[31,32]

Type of Stability Studies and Conditions

- **Chemical stability:** The product should maintain its chemical integrity and potency throughout its shelf life.
- **Physical stability:** The product's appearance, drug content, and dissolution should remain intact.
- **Microbiological stability:** The product should retain sterility, and the effectiveness of antimicrobial agents should be maintained.
- **Therapeutic stability:** The drug's action or therapeutic effect should remain unchanged.
- **Toxicological stability:** There should be no significant increase in toxicity observed.

Stability Studies of Nanocrystal

The long-term stabilities were conducted following ICH Q1A (R2) guidelines, for stability testing of a new drug substance and product. For context with present study, long-term stabilities of nanocrystals were evaluated at a controlled temperature of 5±3°C. The stability parameters were particle size, zeta potential, PDI, drug assay and *in vitro* dissolution profiles.

Stability Parameters

The stability studies are crucial in pharmaceutical development to ensure that drug products remain safe, effective and of adequate quality throughout their shelf life. The following list of parameters for each dosage form is presented as a guide for the types of tests to be included in a stability study. Stability tests are appearance, assay and degradation of products, dissolution, microbial contamination, particle size distribution, preservatives and antioxidant content.

Drug Assay

Stability studies were conducted on the optimized nanocrystal of HTZ (AF2). The optimized batch was stored in a pressure-capped polymeric bag under two different conditions: room temperature (25°C±0.5°C) and elevated temperature (40°C±1°C) with 75±5% RH. Samples were collected at regular intervals of 7 days, 30 weeks and 60 days. The degradation rate constant (K) determined by using the following equation:

$$K = 2.303/t \times \log (CoCt)$$

Shelf life (T10) was determined using the equation……..1

$$\text{Shelf Life } (T10) = 0.104/ K$$

Half-life ($t_{1/2}$) was determined by using the equation…… ….2

$$\text{Half Life } (t_{1/2}) = 0.693/ K$$

Physical Appearance

No changes in the physical appearance were observed when NC formulations were stored at room temperature and 40±1°C upto two months. Degradation kinetics of HTZ in NCs formulation stored at 25±0.5°C and 40±1°C 75±5% RH is shown in Figure 2.[33]

DISCUSSION

Five NC formulations of HTZ (AF1-AF5) were prepared with and without stabilizer as excipient. These batches were then subjected to characterization including particle size, zeta potential, and PDI measurement. NC had nano-size range and possessed physical stability. HTZ did not interact with added stabilizers viz. mannitol and IPA. NC formulations showed compatibility between HTZ and stabilizers. HTZ dissolution rate in NC was improved at 0.1N HCl medium. Optimized formulation (AF2) had 98% of

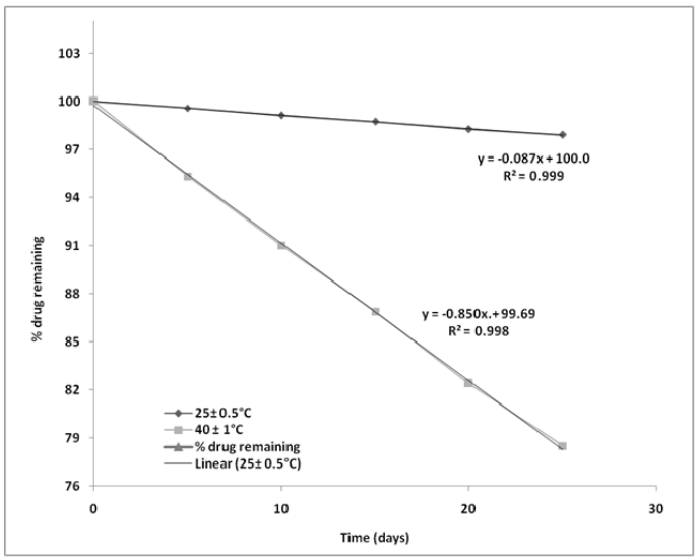

Figure 2: Degradation kinetics of Hydrochlorothiazide stored at 25±0.5ºC and 40±1ºC 75±5% RH.

drug release in 30 min which follows Higuchi kinetics. AF1 had lowest drug release 87.58±1.86% whereas optimized nanocrystal (AF2) of HTZ had highest 97.52±0.7 in the HCl buffer. Further, NCs possessed higher solubility in comparison to the pure HTZ and can be attributed for improved dissolution profile in NCs. Optimized NC (AF2) was stable for the period of two months when stored at (25±0.5ºC) and elevated temperature (40±1ºC) with 75±5% RH. During the study, physical appearance of optimized formulation (AF2) was remained unchanged However, the drug assay in case of AF2 slightly decreased over the time at room temperature (25±0.5ºC), while it exhibited a higher degradation rate at the elevated temperature.

CONCLUSION

Nanocrystals of hydrochlorothiazide fabricated without stabilizer were successfully developed. NC (AF2) was found more stable and exhibited HTZ release (98% in 30 min) with higuchi model of release kinetics.

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CONFLICT OF INTEREST

Authors state that they have no conflict of interest. It means that there are no financial, personal, or professional relationships or circumstances that could potentially bias their work or influence their interpretation of the results.

ABBREVIATIONS

HTZ: Hydrochlorothiazide; **IPA:** Isopropyl Alcohol; **SEM:** Scanning Electron Microscopy; **mL:** Milliliter; **ºC:** Degree Centigrade; **mg:** Milligram; **nm:** Nanometer; **RH:** Relative Humidity.

SUMMARY

To improved the dissolution rate of HTZs through nanocrystals technology.

Two approaches were employed to generate nanocrystals (NCs) using precipitation method with or without stabilizers. NCs were subjected to FTIR, DSC, SEM, zeta-potential and in vitro release characterization.

Physical characterization showed that NCs had particle size in range of nanoscale, improved drug dissolution rate and exhibited storage stability for extended period of time.

Nanocrystals of HTZ harvested without stabilizers had improved drug dissolution rate and storage stability.

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