

FORMULATION AND EVALUATION OF MIXED HYDROTROPIC SOLID DISPERSION OF HYDROCHLORTHAZIDE

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ABSTRACT

For increasing the therapeutic effectiveness of drugs having dissolution rate limited absorption improvement in their water solubility is essential. In the present work mixed hydrotropic solid dispersion of very slightly water soluble drug Hydrochlorthiazide was prepared in order to enhance its solubility. Sodium citrate, niacinamide and polyethylene glycol 4000 were used in different proportions for the preparation of mixed hydrotropic solid dispersion of Hydrochlorthiazide. The Highest solubility enhancement ratio was obtained when Hydrochlorthiazide was mixed with 1:1:1 blend of sodium citrate, niacinamide and polyethylene glycol 4000. For that reason solid dispersion prepared using 1:1:1 blend of sodium citrate, niacinamide and polyethylene glycol 4000 was used for scanning electron microscopy, *in vitro* dissolution study, differential scanning calorimetry and X ray diffraction analysis. Mixed hydrotropic solid dispersions were tested for stability according to ICH guidelines. Rough, disordered and intact structures of solid dispersion might be helpful for increasing the dissolution of Hydrochlorthiazide when come in contact aqueous fluid. Crystalline nature of Hydrochlorthiazide was confirmed through the sharp and intense peaks of Hydrochlorthiazide on XRD. Differential scanning calorimetry graphs indicated complete dispersion of Hydrochlorthiazide in the mixture of hydrotropic solvents. Solid dispersions were found to be effective in releasing Hydrochlorthiazide at higher rate in comparison to pure Hydrochlorthiazide and physical mixture of Hydrochlorthiazide. All formulations were found to be chemically stable at higher temperature.

Kew words: Hydrotropic solubilization, Hydrochlorthiazide, solid dispersion

INTRODUCTION

Product development scientists frequently meet significant difficulties in solving the problem of poor water solubility of drug applicant in the growth of pharmaceutical dosage form. A couple of decades back, 40% modern drug disappointment in development had been recognized poor biopharmaceutical properties, as well as poor water solubility. A solid dispersion of one or more active pharmaceutical ingredients in an inert and nontoxic carrier matrix is prepared by using solvent evaporation method, melting-solvent method, fusion method^{1,2}. Drugs with having low aqueous solubility will mostly show less dissolution rate, as well as incomplete absorption and drugs with having poor membrane permeability, will exhibit penetration rate-limited absorption.

Hydrotropic solid dispersion methods prohibit the use of organic solvent for the formulation of solid dispersion³. Hydrotropic agents have water solubility, whereas the drug has poorly water solubility. In the presence of a large amount of hydrotropic agents in the water, the drugs get solubilized. After that, water is evaporated by a suitable evaporation method to get a solid mass that is solid dispersion. Then, prepared solid dispersions can be denoted as hydrotropic solid dispersions. Advantages of this method are the solvent character is independent of pH, has high selectivity and does not require emulsification. There is no need of chemical modification of water insoluble drug. Sodium benzoate, sodium acetate, sodium bicarbonate, sodium chloride, sodium gluconate, thiourea, trisodium citrate and urea have been employed to enhance the aqueous solubility of many poorly water soluble drugs.

Newly developed mixed hydrotropic solid dispersion technology was used in the present research. In this method two or more hydrotropic blends were used which may give remarkable synergistic enhancement effect on solubility of poorly water soluble drugs. The individual concentration of hydrotropic agents may be reduced in the formulation of dosage forms of hydrophobic drugs using this technique. Therefore, side effects associated with individual large concentration of hydrotropic agents are minimized⁴.

For the present research work Hydrochlorthiazide, a slightly water soluble drug was selected. Hydrochlorthiazide is a diuretic. It enhances the formation of urine and thus enhance the excretion of waste materials from the body.

MATERIALS AND METHODS

MATERIALS

PEG 4000, niacinamide, sodium citrate and other chemicals were purchased from Vijay Scientific Centre, Gwalior. Hydrochlorthiazide was found as a gift sample from Cipla Ltd., Mumbai.

METHODS

Solubilization studies

Determination of equilibrium solubility of Hydrochlorthiazide in distilled water

Sufficient excess amount of Hydrochlorthiazide was mixed with 10 ml of distilled water in screw capped amber colored glass vials. The vial was shaken mechanically for 12 hours at room temperature in wrist action shaker. The solution was allowed to equilibrate for next 24 hours and then centrifuged for 5 minutes at 2000 rpm using a centrifuge (Remi Instruments Limited, Mumbai, India). The supernatant of vial was separated by filtration through what man filter paper # 1. An aliquot of filtrate was diluted suitably with distilled water and analyzed spectrophotometrically at 269 nm corresponding λ_{\max} of Hydrochlorthiazide⁵.

Selection of hydrotropic agents

In order to select suitable hydrotropic agents for sufficient enhancement in solubility an approximate solubility determination method was used. A lot of hydrotropic agents, sodium benzoate, sodium citrate, sodium acetate, PEG 4000, urea, niacinamide and sodium ascorbate with moderately high concentrations (10-40%) were tried out on the basis of literature survey.

Twenty five ml of hydrotropic solution was taken in a 50 ml glass bottle and total weight (including the cap) was noted down. Then, few mg (by visual observation) of fine powder of Hydrochlorthiazide was added to the bottle. This bottle was agitated vigorously (by hand). When drug got dissolved, more drug (few mg by visual observation) was added to the bottle and again the bottle was agitated vigorously. Same process was repeated till some excess Hydrochlorthiazide remained undissolved (after constant vigorous agitation for 10 minutes). Then again total weight was noted down. From the difference in two readings (of weight), an approximate solubility and solubility enhancement ratios (solubility in hydrotropic solution/solubility in distilled water) were determined. When the solubility enhancement ratio value of drug was found to be 5 or more, such hydrotropic solution was chosen for further studies of the drug.

Determination of equilibrium solubility of Hydrochlorthiazide in different concentration of hydrotropic agent solutions

Aqueous solutions of chosen hydrotropic agents (sodium citrate, niacinamide and PEG 4000 of known concentrations (10%, 20%, 30%, and 40%) were prepared in distilled water. Equilibrium solubility of Hydrochlorthiazide was determined using the method mentioned previously for the estimation of solubility in distilled water.

Determination of equilibrium solubility of drug in blends of hydrotropic agents

Aqueous solubility of Hydrochlorthiazide was estimated in different blends of hydrotropic agents using the equilibrium solubility method.

$$\text{Solubility enhancement ratio} = \frac{\text{Solubility in particular hydrotropic solution}}{\text{Solubility in distilled water}}$$

Blend CNP (sodium citrate, niacinamide and PEG 4000 1:1:1) was found to be most prominent in enhancing solubility of Hydrochlorthiazide in water. Therefore it was chosen to prepare physical mixture and solid dispersion of Hydrochlorthiazide⁵.

Formulation Development

Preparation of Physical mixture of Hydrochlorthiazide

Hydrochlorthiazide and blend of hydrotropic agents CNP(1:1:1) were accurately weighed and shifted to a glass pestle and mortar and mixed for 10 min with intensive trituration. Then, powder mass was passed through sieve number 60. After this, the physical mixture was kept in desiccator for 24 h and then stored in air-tight glass bottles. Composition of physical mixture is given in table 1.

Table 1: composition of physical mixture of Hydrochlorthiazide

| Formulation code | Ratio of drug: blend CNP | Quantity of drug (g) | Quantity of hydrotropes (g) | | |
|------------------|--------------------------|----------------------|-----------------------------|-------------|----------|
| | | | Sodium citrate | Niacinamide | PEG 4000 |
| PM | 1:10 | 2 | 6.66 | 6.66 | 6.66 |

Preparation of solid dispersion of Hydrochlorthiazide ⁶

The hydrotropic agents were dissolved in minimum possible amount of distilled water. Hydrochlorthiazide was weighed and mixed with water in the beaker. This mixture now placed on a magnetic stirrer and then stirred until most of the water gets evaporated. Now this mixture was spread on several watch glasses to the hasten drying of hydrotropic mixture. After drying, the hydrotropic mixture, it was scrapped using spatula and the mixture was shifted to desiccator to eliminate the remaining moisture. The hydrotropic mixture was stored in amber colored screw capped bottles until further evaluation. Composition of solid dispersion prepared using different ratio of Hydrochlorthiazide and hydrotropic agents is given in table 2.

Table 2: composition of solid dispersion formulations of Hydrochlorthiazide

| S. No. | Formulation code | Ratio of Hydrochlorthiazide: blend CNP (1:1:1) | Quantity of Hydrochlorthiazide (g) | Quantity of hydrotropic agents (g) | | |
|--------|------------------|--|------------------------------------|------------------------------------|-------------|----------|
| | | | | Sodium citrate | Niacinamide | PEG 4000 |
| 1 | HTZ1 | 1:6 | 2 | 4 | 4 | 4 |
| 2 | HTZ 2 | 1:8 | 2 | 5.33 | 5.33 | 5.33 |
| 3 | HTZ 3 | 1:10 | 2 | 6.66 | 6.66 | 6.66 |

Evaluation

Percentage Yield⁷

Practical yield was calculated to determine the percent yield or efficiency of any method in the preparation of solid dispersions, thus it is helpful in the selection of suitable method of production. It was calculated using the following formula:

$$\text{Percentage yield} = \frac{\text{Practical Yield}}{\text{Theoretical yield}} \times 100$$

Particle size analysis:⁸

The size distribution in terms of average diameter (d_{avg}) of the mixed hydrotropic solid dispersions was estimated using optical microscopic method. A compound microscope fitted with a calibrated ocular micrometer and a stage micrometer slide was used to count minimum 100 particles.

Drug content:⁹

The 25 mg of powdered solid dispersion of Hydrochlorthiazide was accurately weighed and shifted to a 25 mL volumetric flask. About 15 mL of simulated gastric fluid (pH 1.2) was added and flask was shaken to dissolve the formulation completely. Then, volume was made up to the mark using simulated gastric fluid (pH 1.2). Then 1 mL of this solution was placed in a 50 mL volumetric flask and then the volume was made up to the mark using simulated gastric fluid (pH 1.2) and absorbance of this solution was taken at wavelength of 266 nm against simulated gastric fluid (pH 1.2) as blank. Corresponding equation of regressed line was used for the determination of drug content.

Bulk density⁹

It is the ratio of total mass of powdered drug sample to the bulk volume of powdered drug sample. For the measurement of bulk density weighed quantity of powdered Hydrochlorothiazide solid dispersion sample was poured into a measuring cylinder and the volume was noted. It is expressed in gm/mL and is given by following formula. It is expressed in gm/ml.

$$\text{Bulk density} = \frac{\text{Mass of powdered sample}}{\text{Bulk volume of powdered sample}}$$

Tapped density⁹

It is the ratio of total mass of powdered drug sample to the tapped volume of powdered drug sample. For the measurement of tapped density an accurately weighed powdered Hydrochlorothiazide solid dispersion sample was carefully added to the graduated cylinder with the aid of funnel. The starting volume was noted and the sample containing graduated cylinder was tapped on a horizontal base. Tapping was proceed until no further reduction in sample volume was seen. Volume was noted down and following formula is utilized for the calculation of tapped density.. It is expressed in gm/ml.

$$\text{Tapped density} = \frac{\text{Mass of powdered sample}}{\text{Tapped volume of powdered sample}}$$

Carr's Index (I)⁹

It expresses the powder compressibility and ease with which a material can be induced to flow and. It is expressed in percentage and is determined by the formula:

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where, D_t is the tapped density of the powdered sample, D_b is the bulk density of the powdered sample.

Angle of Repose¹⁰

A funnel was fixed at a height of approximately of 2-4 cm over the platform. The sample was gradually passed along the wall of funnel, till the cone of the powder shaped. Angle of repose was calculated by measuring the height of the cone of powder and radius of the heap of the powdered drug sample. Angle of repose is determined by the following formula:

$$\theta = \tan^{-1} \frac{h}{r}$$

Where, θ = angle of repose, h = height of the cone, r = radius of heap.

Scanning Electron Microscopy (SEM)¹¹

The surface morphology of Hydrochlorothiazide, selected hydrotropic agents and solid dispersion HTZ3 was determined using an analytical scanning electron microscope (LEO-435VP, Leo Co. Ltd, UK). The samples were gently sprinkled on a double-sided adhesive tape pasted to an aluminum stub. The stubs were then coated with platinum to a thickness of about 10Å under an argon atmosphere using a gold-sputter module in a high-vacuum evaporator. Later, the stubs containing the coated samples were placed in the scanning electron microscope chamber. The coated samples were then randomly scanned and photomicrographs were taken.

In vitro dissolution study¹²

In vitro dissolution studies of Hydrochlorothiazide, physical mixture and mixed hydrotropic solid dispersion HTZ3 were performed in a USP standard dissolution test apparatus-II (Jyoti scientific industries, India) employing a paddle stirrer at 75 rpm using 900 mL of simulated gastric fluid (pH 1.2) at 37±0.5°C as dissolution medium. Same procedure was followed to assess the dissolution profile of Hydrochlorothiazide physical mixture and mixed hydrotropic solid dispersion HTZ3 in SIF (pH 6.8).

Differential scanning calorimetry¹³

Differential scanning calorimetry analysis was performed using a differential scanning calorimeter (Jade, PerkinElmer, USA). Weighed samples (4.3 mg) of Hydrochlorothiazide, prepared mixed hydrotropic solid dispersions and selected hydrotropic agents were heated in hermetically sealed aluminum pans over a temperature range of 30-300°C at a constant rate of 10°C/min.

X-ray diffraction analysis¹⁴

The powder X-ray diffraction spectra of Hydrochlorthiazide, prepared mixed hydrotropic solid dispersions and selected hydrotropic agents were obtained using RU-H R, Horizontal Rotaflex rotating anode X-ray generator instrument, Rigaku (Rigaku International Corporation, Tokyo, Japan). The sample was spread on a graticule and pressed in such a way that sample did not fall on keeping the graticule vertical. The graticule was placed in sample holder and exposed to C K -radiation (40 KV, 50 MA), $2\theta=5^\circ$ to 40° at a scanning speed of $4^\circ/\text{min}$ and step size $0.02^\circ 2\theta$.

Stability studies of drug formulations^{15,16,17}

The pharmaceutical product development requires a variety of logical ability to build-in quality, adequacy and safety. Key steps on the way of product development incorporates pharmaceutical analysis and stability studies that are required to decide and guarantee the identity, strength and purity of ingredients, as well as those of the formulations.

The stability of a product may be characterized as the degree to which a product holds, within specified limits, all through its period of storage and utilize, the same properties and characteristics hold at the time of its packaging. The characteristics incorporate physical, chemical, microbiological, therapeutic and toxic properties and all are required to stay within acceptable limits till the time of use of the product by a patient. Stability testing measures and documents the ability of a product to hold its potency prior to its predicted expiration date. Stability data also play a key role in determining labeling instructions. These are also a requirement for manufacturing of regulatory approved drug products.

Stability focuses on the chemical (i.e. integrity, strength, degradation) and physical properties (e.g. appearance, hardness, particle size, solubility) of active pharmaceutical ingredients and products. In addition, microbiological testing is done to ensure that the drug substances and products maintain their resistance to microbial and bacterial growth. An all- encompassing testing is used to evaluate and verify the identity, potency and availability of active pharmaceutical ingredients in the product.

All medicated products decompose with time. Instabilities in modern formulations are often detectable only after considerable storage periods under normal conditions. To assess the stability of a formulated product it is usual to expose it to 'high stresses, i.e. conditions of temperature, humidity and light intensity that are known from experience to be likely causes of breakdown. High stress conditions enhance the deterioration of the product and therefore reduce the time required for testing. This enables more data to be gathered in a shorter time, which in turn will allow unsatisfactory formulations to be eliminated early in a study and will also reduce the time for a successful product to reach the market. It must be emphasized that extrapolations to normal' storage conditions must be made with care and that the formulator must be beyond any doubt that such extrapolations are valid. It is advisable therefore to run concurrently a batch under expected normal conditions to confirm later that these assumptions are valid. Good formulations will invariably break down more slowly than poor ones.

Chemical stability testing of mixed hydrotropic solid dispersions

Different hydrotropic solid dispersions were subjected to chemical stability testing. Powders of various formulations were kept in 10 ml colourless glass vials and vials were plugged and sealed. Vials were kept at room temperature, at 55°C in oven and at 40°C with 75% RH in ICH certified stability chamber. The samples were withdrawn at different time intervals and drug contents were determined spectrophotometrically. To calculate the drug content, the formulations were analyzed by the same procedures which were applied to determine their drug contents after their formulations. The initial drug content for each formulation was considered as 100.00%.

RESULTS AND DISCUSSION

Solubilization studies

Determination of equilibrium solubility of drug in distilled water

Solubility of Hydrochlorthiazide in distilled water was found to be 0.0.65 mg/ml.

Selection of ratios of drug and carrier for formulation development

On the basis of the results obtained from the approximate solubility determination study, the following three hydrotropes were selected.

- a) Sodium citrate
- b) Niacinamide

c) PEG 4000

Determination of equilibrium solubility of Hydrochlorthiazide in different concentration of hydrotropic agent solutions

Table 3: Equilibrium solubility data of Hydrochlorthiazide in different concentration of hydrotropic solution

| Name of hydrotropic agent | Particular | 10 % | 20 % | 30 % | 40 % |
|---------------------------|------------------------------|-------|-------|--------|--------|
| SC | Equilibrium solubility | 2.26 | 3.31 | 4.28 | 5.31 |
| | Solubility enhancement ratio | 28.25 | 41.37 | 53.50 | 66.37 |
| NM | Equilibrium solubility | 1.23 | 1.92 | 2.68 | 3.51 |
| | Solubility enhancement ratio | 15.37 | 24 | 33.5 | 43.87 |
| P4 | Equilibrium solubility | 3.18 | 5.82 | 8.61 | 11.26 |
| | Solubility enhancement ratio | 39.75 | 72.75 | 107.62 | 140.75 |

Table 4: Equilibrium solubility data of Hydrochlorthiazide in different hydrotropic blends

| Name and concentration of hydrotropic agent | Equilibrium solubility | Solubility enhancement ratio |
|---|------------------------|------------------------------|
| SC (20%) + NM (20 %) | 4.85 | 60.62 |
| SC (20%) + P4 (20%) | 12.43 | 155.37 |
| NM (20 %) + P4 (20%) | 9.03 | 112.87 |
| SC (13.3 %) + NM (13.3 %) + P4 (13.3%) | 14.73 | 184.12 |

Equilibrium solubility data revealed that highest solubility was obtained in case of mixture of all there hydrotropic agents (sodium citrate, niacinamide and PEG 4000 in the ratio of 1:1:1).

Table 5: Practical yield, average particle size and drug content of mixed hydrotropic solid dispersion of Hydrochlorthiazide

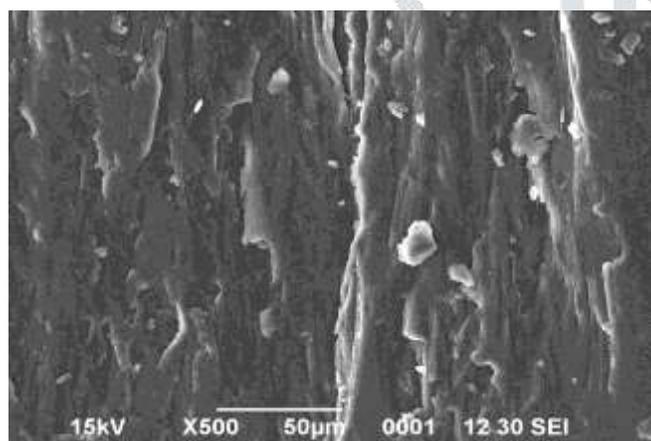
| Solid dispersion formulation | Practical yield (%) | Average particle size (µg/ml) | Drug content (%) |
|------------------------------|---------------------|-------------------------------|------------------|
| NF1 | 99 | 62.6 | 98 |
| NF2 | 97 | 57 | 98.4 |

| | | | |
|-----|------|------|----|
| NF3 | 98.6 | 61.4 | 96 |
|-----|------|------|----|

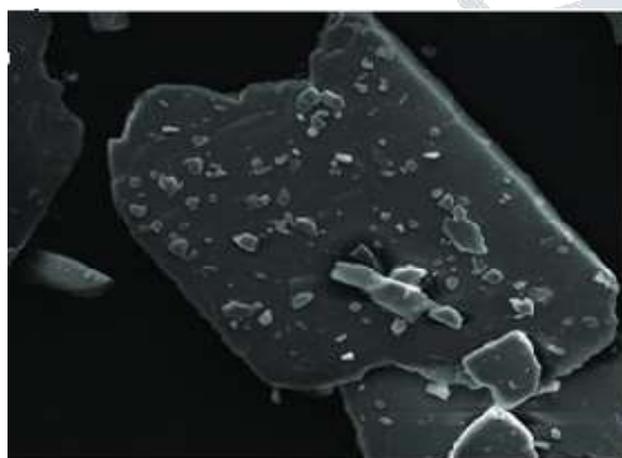
Table 6: Flow characteristics of solid dispersion of Hydrochlorthiazide

| Mixed hydrotropic solid dispersion formulation | Bulk density (g/ml) | Tapped density (g/ml) | Carr's index | Angle of repose (°) |
|--|---------------------|-----------------------|--------------|---------------------|
| NF1 | 0.56 | 0.67 | 16.41 | 23.3 |
| NF2 | 0.62 | 0.73 | 15.07 | 24 |
| NF3 | 0.58 | 0.69 | 15.94 | 22.6 |

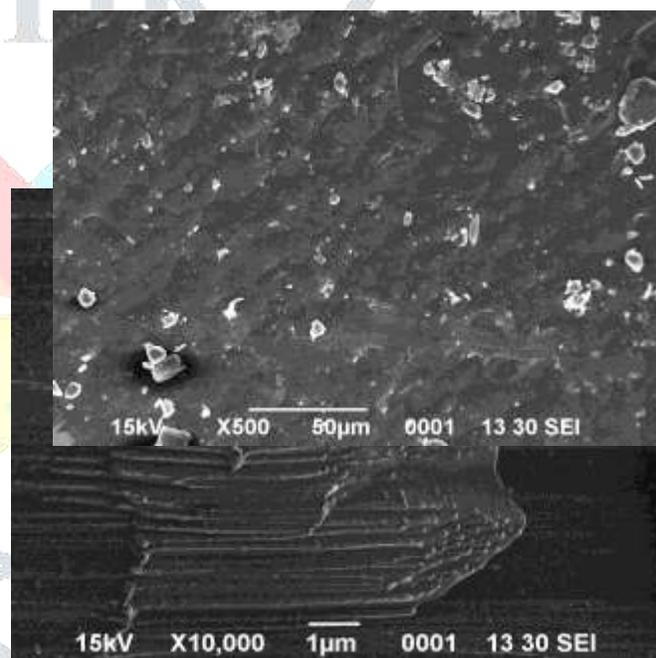
Values of Carr's index and angle of repose revealed good flow properties of all three formulations.



Micrographs



1- Scanning electron micrograph of Hydrochlorthiazide



SEM

Fig.

Fig. 2- Scanning electron micrograph of Niacinamide

Fig. 3- Scanning electron micrograph of PEG 4000

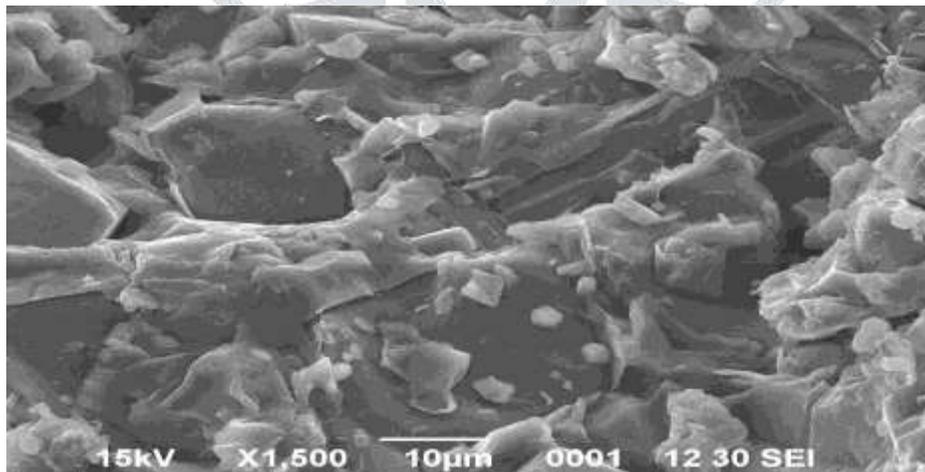
Fig. 4- Scanning electron micrograph of Sodium citrate

Fig. 5- Scanning electron micrograph of Solid dispersion [1: 10 Hydrochlorthiazide: CNP (1:1:1) blend]

Surface micrographs of prepared mixed hydrotropic solid dispersions and pure Hydrochlorthiazide were determined using SEM technique. The SEM micrograph of pure Hydrochlorthiazide showed large crystalline forms of Hydrochlorthiazide agglomerates with ordered shape and size in Fig.1. SEM of solid dispersion prepared using interaction of Hydrochlorthiazide and hydrotropic agents. The particle size of combined matrix showed marked decrease in size. The surface characteristics of solid dispersions show rough disordered and intact structures, which subsequently help to dissolve drug when comes in contact with aqueous fluid.

In vitro dissolution study

Table 7: Cumulative % drug release from physical mixture and solid dispersions of Hydrochlorthiazide in simulated gastric fluid (pH 1.2)



| Time in min. | Cumulative % drug release from pure drug, physical mixture and solid dispersions of Hydrochlorthiazide in simulated gastric fluid (pH 1.2) | | | | |
|--------------|--|----|-----|-----|-----|
| | Hydrochlorthiazide | PM | NF1 | NF2 | NF3 |
| 0 | 0 | 0 | 0 | 0 | 0 |

| | | | | | |
|----|------|------|------|------|------|
| 10 | 5 | 12.3 | 19 | 28.6 | 30.2 |
| 20 | 9.4 | 18.4 | 39.4 | 45.2 | 49.8 |
| 30 | 15 | 21.5 | 58.2 | 63.5 | 67.6 |
| 40 | 17.6 | 23.6 | 64.9 | 66.8 | 72.3 |
| 50 | 18.5 | 24.8 | 71.3 | 77.2 | 78.5 |
| 60 | 20.2 | 26.7 | 73.7 | 79 | 81.7 |
| 70 | 24 | 35 | 82 | 88 | 91 |
| 80 | 26 | 44 | 97 | 98.1 | 99.2 |

(Mean \pm SD, n=3)

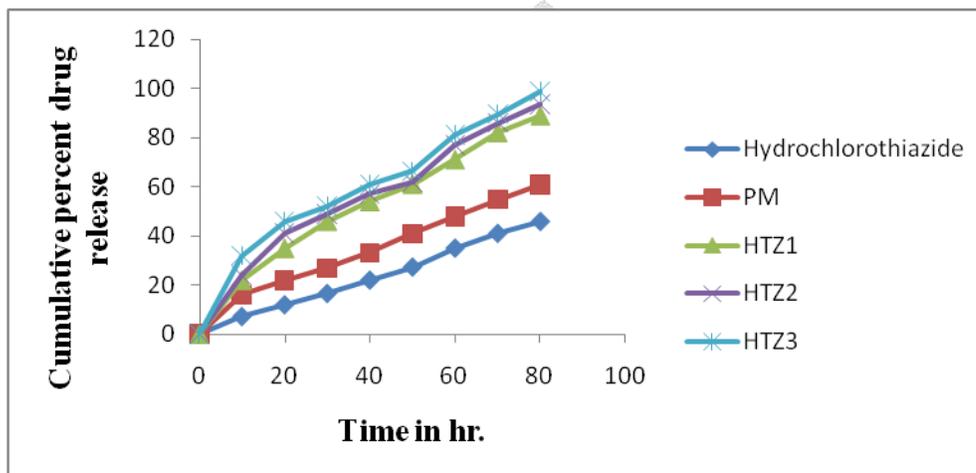


Figure 6- Cumulative % drug release from pure drug, physical mixture and solid dispersions of Hydrochlorothiazide in simulated gastric fluid (pH 1.2)

Table 8: Cumulative % drug release from physical mixture and solid dispersions of Hydrochlorothiazide in SIF (pH 6.8)

| Time (min) | Cumulative % drug release from physical mixture and solid dispersions of Hydrochlorothiazide in SIF (pH 6.8) | | | | |
|------------|--|------|-----|-----|------|
| | Hydrochlorothiazide | PM | NF1 | NF2 | NF3 |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 10 | 7.2 | 16 | 22 | 24 | 32 |
| 20 | 12 | 22 | 35 | 41 | 46 |
| 30 | 16.6 | 27 | 46 | 49 | 52 |
| 40 | 22 | 33.2 | 54 | 57 | 61 |
| 50 | 27.3 | 41 | 61 | 62 | 66.4 |
| 60 | 35 | 48 | 71 | 77 | 81 |

| | | | | | |
|----|------|------|------|------|------|
| 70 | 41 | 55 | 82 | 86 | 89.6 |
| 80 | 45.8 | 61.1 | 88.9 | 93.6 | 98.9 |

(Mean ± SD, n=3)

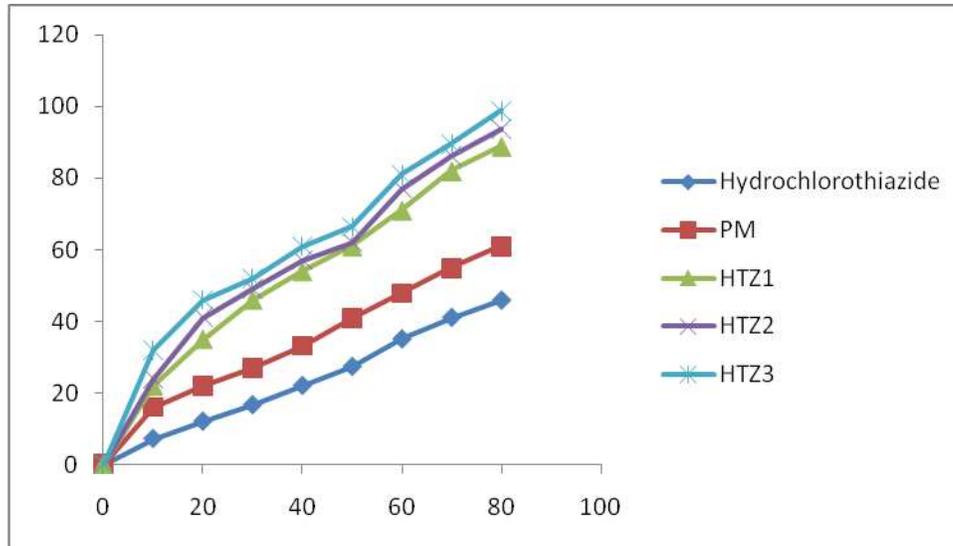


Figure 7-Cumulative % drug release from pure drug, physical mixture and solid dispersions of Hydrochlorthiazide in SIF (pH 6.8)

From tables (Table 7 and Table 8) and figures (Fig.6 and Fig.7), drug release rate was found to be in following order:

Pure Hydrochlorthiazide < physical mixture < Mixed hydrotropic solid dispersions of Hydrochlorthiazide
 The reason behind highest drug release rate from mixed hydrotropic solid dispersion might be reduction in particle size of combined matrix of Hydrochlorthiazide and hydrotropic agents. In comparison to pure Hydrochlorthiazide, the dissolution rate of physical mixtures was slightly increased probably because the hydrotropic agents can wet the surface of Hydrochlorthiazide particles and acts to solubilize them. It was also observed that on increasing the concentration of solubilizing agent dissolution behavior was improved. Because of above mentioned reason quick onset of action obtained in case of mixed hydrotropic solid dispersion of Hydrochlorthiazide.

DSC micrographs

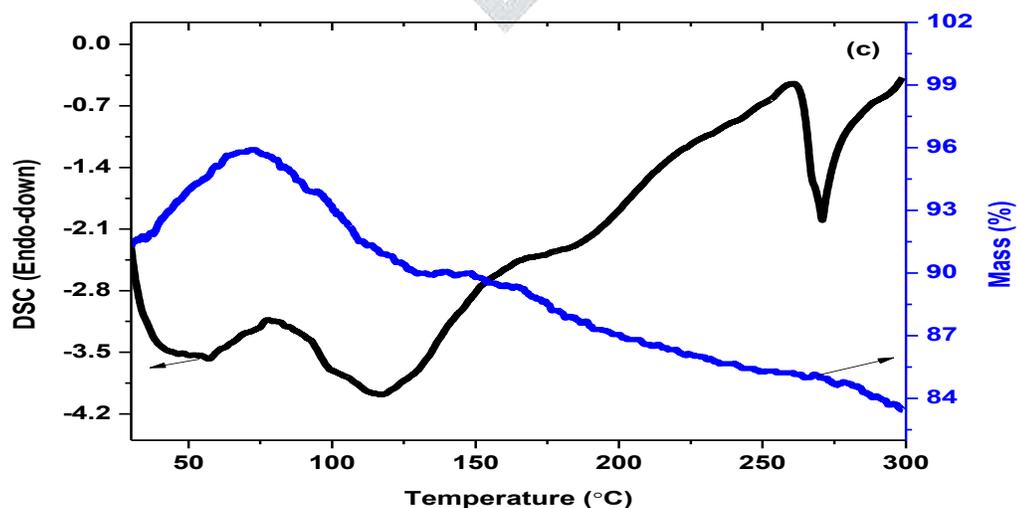


Fig. 6 - DSC Graph of Hydrochlorthiazidee

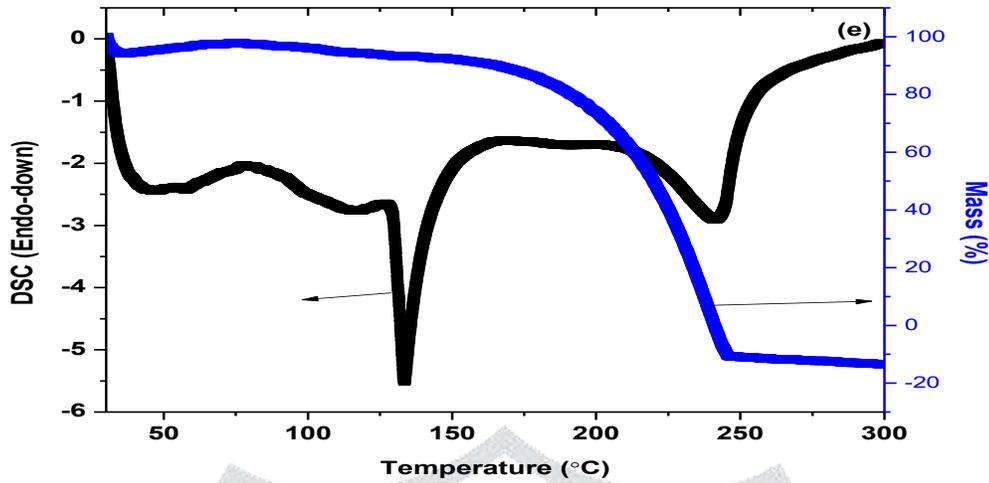


Fig. 7 - DSC Graph of Niacinamide

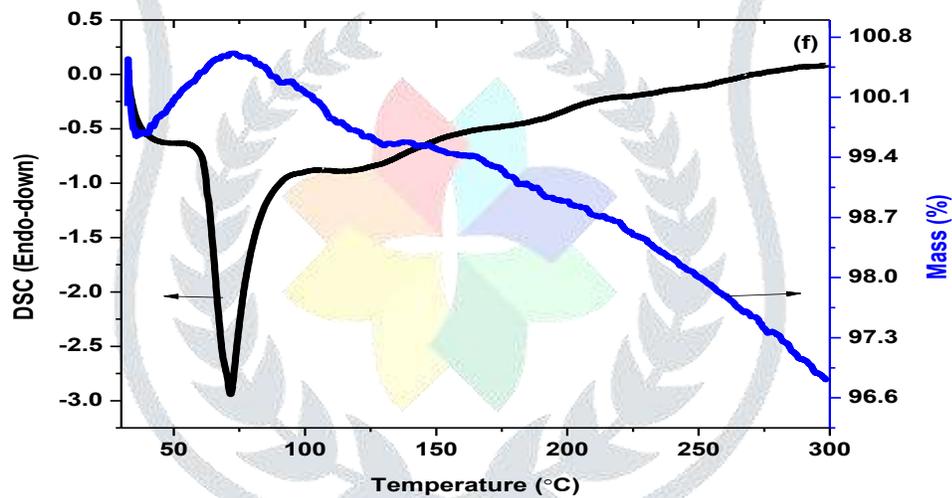


Fig. 8 - DSC Graph of PEG 4000

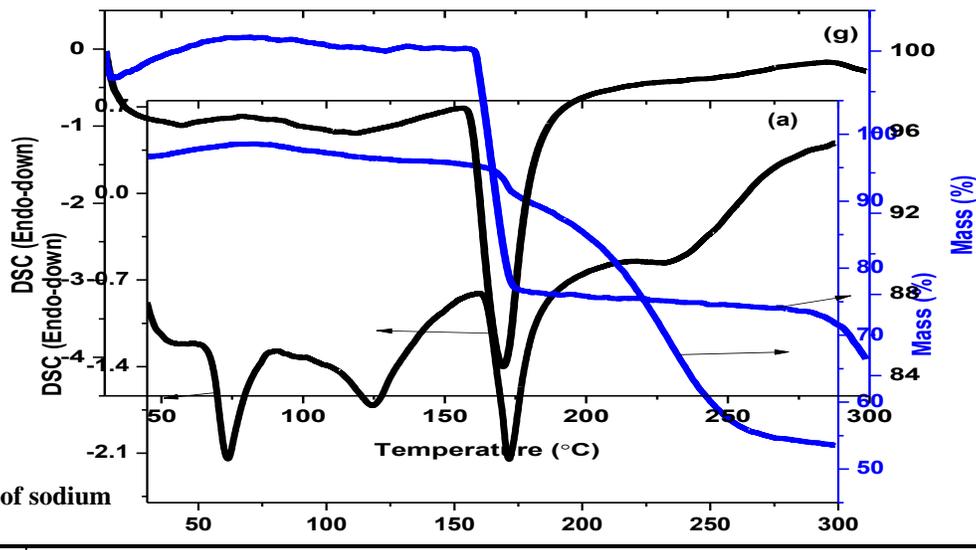


Fig. 9- DSC Graph of sodium

citrate

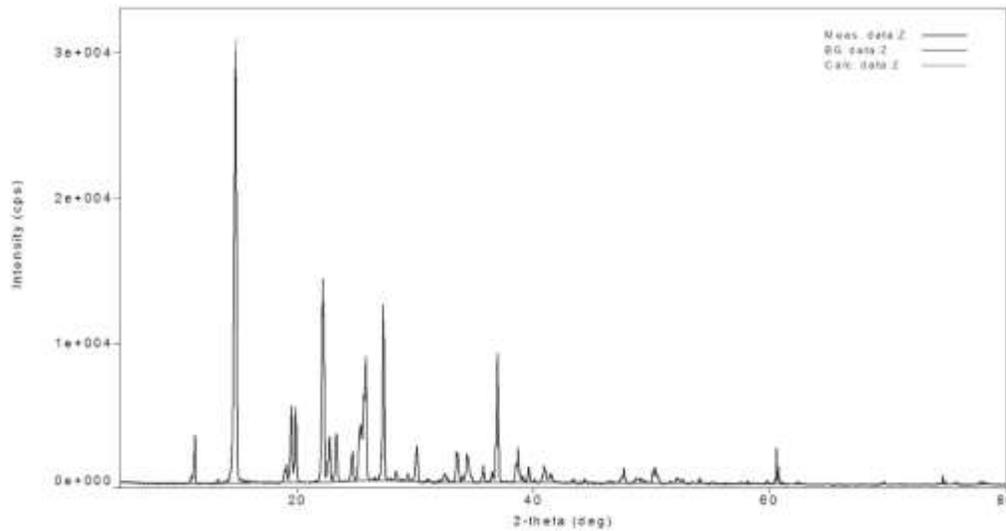


Fig. 10 – DSC Graph of SOLID DISPERSION [1: 10 Hydrochlorthiazide: CNP (1:1:1) blend]

The DSC curve for Hydrochlorthiazide showed a sharp melting peak at 221°C which corresponds to its melting point. This is indicative of the crystalline nature of the drug. The DSC curve for niacinamide showed a peak at 135°C, PEG 4000 shows a peak on 79°C, sodium citrate shows a peak on 300° C which corresponds to their melting points. The DSC curve for the 1: 10 Hydrochlorthiazide: CNP showed a peak at 174 °C but did not show any peak at 221°C. The disappearance of the endothermic peak at 221°C indicates that the drug is dispersed in the mixture of hydrotropic solvents. Thus the DSC studies indicate the formation of solid dispersion of Hydrochlorthiazide for CNP (1:1:1) in the ratio of 1:10 which is evident by the appearance of one peak in the DSC profile for the solid dispersions.

X-ray diffraction analysis¹⁶

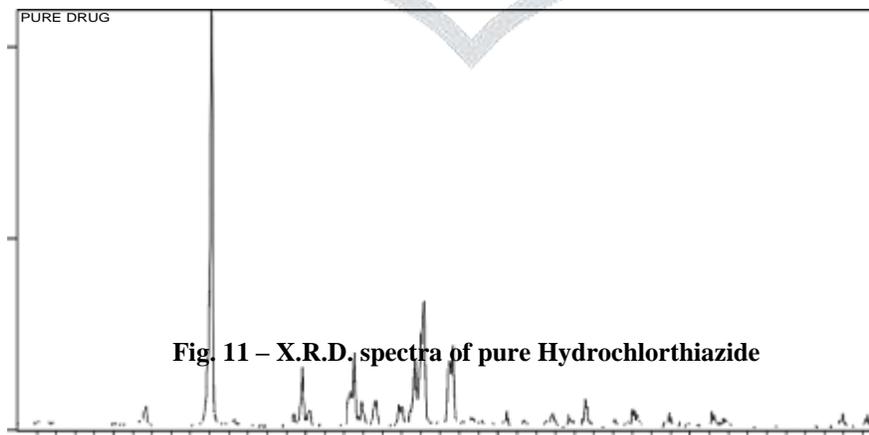


Fig. 11 – X.R.D. spectra of pure Hydrochlorthiazide

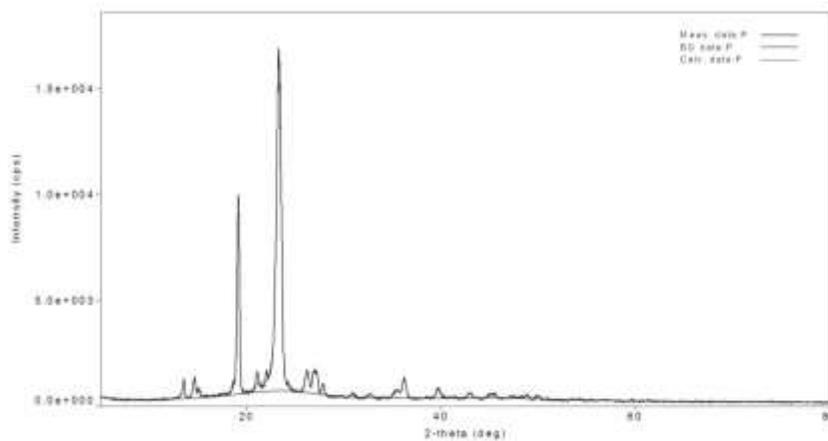


Fig. 12 – X.R.D.

spectra of niacinamide

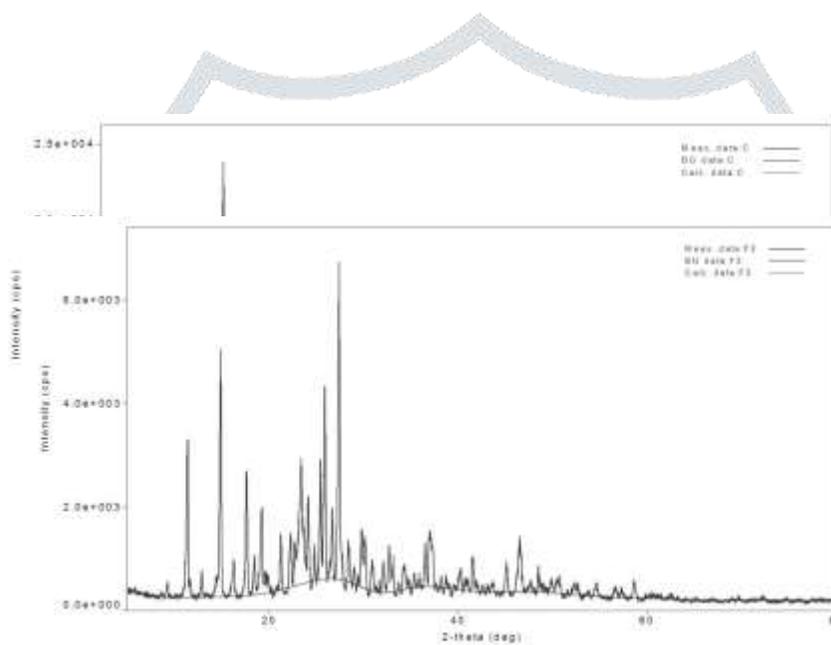


Fig. 13 – X.R.D.

spectra of PEG 4000

Fig. 14 – X.R.D. spectra of sodium citrate

Fig. 14 – X.R.D. spectra of sodium citrate

The X.R.D. pattern of Hydrochlorthiazide showed intense and sharp peaks that prove crystalline nature of Hydrochlorthiazide. Also X.R.D. patterns of solid dispersion gave sharp and intense peaks and are thus easily comparable with that of pure Hydrochlorthiazide.

STABILITY STUDIES

Table 9: Chemical stability data of Hydrochlorthiazide hydrotropic solid dispersions and physical mixture (n=3)

| Condition | Time (months) | Percent residual drug in formulations (mean ± S.D.) | | |
|------------------|---------------|---|---------------|---------------|
| | | NF1 | NF2 | NF3 |
| Room temperature | 1 | 99.63 ± 0.868 | 99.76 ± 2.307 | 99.69 ± 1.330 |
| Room temperature | 3 | 99.36 ± 0.720 | 99.26 ± 1.131 | 99.21 ± 1.992 |
| Room temperature | 6 | 99.13 ± 0.568 | 99.16 ± 1.107 | 99.19 ± 1.330 |
| 40°C/75% RH | 1 | 98.56 ± 0.720 | 98.76 ± 1.131 | 98.51 ± 0.992 |
| 40°C/75% RH | 3 | 98.51 ± 0.868 | 98.51 ± 2.307 | 98.39 ± 1.330 |
| 40°C/75% RH | 6 | 98.36 ± 0.720 | 98.26 ± 1.131 | 98.21 ± 0.992 |
| 55°C | 1 | 98.33 ± 0.868 | 98.76 ± 2.307 | 98.69 ± 1.330 |
| 55°C | 3 | 97.36 ± 0.720 | 97.26 ± 1.131 | 97.21 ± 0.992 |
| 55°C | 6 | 97.12 ± 0.720 | 97.16 ± 1.131 | 97.11 ± 0.992 |

(Mean ± SD, n=3)

Good chemical stability of all formulations after storage for 6 months at room temperature was proved by the value of the residual drug content that was above 98% (much above 90.00%), The residual drug contents after storage for 6 months at 40°C/75% RH in all formulations was above 96%, showing good chemical stabilities at moderate temperature. The residual drug content after storage for 6 months at 55°C in all formulations was above 97.00%, showing good chemical stabilities at a higher temperature.

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