Introducing hydrochlorothiazide drug for solubility enhancement by Novel hybridization technique

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Abstract: **Solubility enhancement of Hydrochlorothiazide drug by novel hybridization technique that has a combinational approach of complexation and liquisolid technique. A complex of hydrochlorothiazide -captisol (1:1 molar ratio) is dispersed in the non-volatile solvent & then the carrier was added into mortar and pestle and then it is mixed with it for 10 to 20 min. Then coating materials are completely mixed with the above mixture to form a free-flowing powder. This free-flowing powder is mixed with other excipients & compressed into tablets by using a tablet compression machine using the same components. This technique also improves the drug release of poorly soluble drugs. Hydrochlorothiazide-Captisol inclusion complex is taken in different ratios (1:1, 1:2 & 1:3). Saturated solutions in 7.4 pH phosphate buffer were prepared. The filtered supernatants were further diluted if necessary with 7.4 pH phosphate buffer and analyzed spectrophotometrically using a UV/visible spectrophotometer (Shimadzu). The solubility of Hydrochlorothiazide in Hydrochlorothiazide-captisol inclusion complex is calculated using the Hyrochlorothiazide calibration. The ratios are compared with one another to find the highest solubility rate.**

INTRODUCTION

Hydrochlorothiazide (HCTZ) is a thiazide-type diuretic that has been used clinically for more than half a century. The drug has been widely used to treat hypertension globally and is relatively very safe. Hydrochlorothiazide acts on the distal convoluted tubules and inhibits the sodium chloride co-transporter system .Hydrochlorothiazide inhibits sodium chloride transport in the distal convoluted tubule. This action leads to a diuretic action that lowers blood pressure, but there is also a potassium loss in the urine. More sodium is then excreted in the kidney with accompanying fluid. Pharmacological effects begin in about 2 hours after an oral dose, peak in 4 hours, and lasts for about 6 to 12 hours. Diuretics, sometimes called water pills, help rid your body of salt (sodium) and water. Novel hybridisation technique is one of the most successful strategies to improve the drug release of poorly soluble drugs and the solid dispersion of drug in a water-soluble polymer has been shown to be one of the most promising strategies to improve solubility. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce their side effects. There are several pharmaceutical strategies available to improve the aqueous solubility of poorly soluble drugs, solid dispersion, solubilization using surfactant, the use of co-solvent, reduction of particle size, hydrotropic and the use of aqueous soluble derivatives or salts. The combination of these two methods is called the novel hybridization technique, which imparts advantages of both the methods and becomes advantageous to improve dissolution efficiency of Hydrochlorothiazide. It belongs to BCS class-IV category. Due to poor solubility in aqueous media, treatment leads to frequent dosing & increasing cost of therapy subsequently. The use of poorly water soluble drugs has a number of drawbacks such as increasing the dosage, administration frequently and the resultant occurance of side effects. The dissolution rate is directly proportional to solubility of drugs. The dissolution rate is the rate limiting factor for class II and class IV drugs as defined in the Biopharmaceutical classification system. The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. Solubility is one of the important parameter to achieve desired concentration of drug present in systemic circulation for pharmacological response. The term water soluble drugs are the drugs which are known as

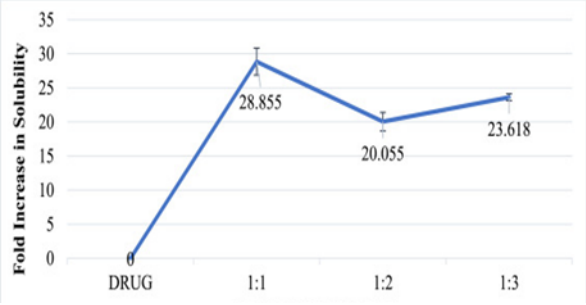
- Sparingly water soluble (1 part solute to 100 parts of water)
- Slightly water soluble (1 into 100 to 1000 parts of water)

- Very slightly water soluble (1 part solute into 1000 to 10,000 parts of water).

MATERIALS AND METHODS

DRUG: Hydrochlorothiazide was purchased from Orchid pharmaceuticals and β-cyclodextrin (Captisol) from Cydex, Gangwal, Mumbai, Maharashtra, India and all other reagents used were of highest purity and analytical grade. Double distilled water was used throughout the experimental work.

PHASE SOLUBILITY STUDIES: The phase solubility studies of Hydrochlorothiazide were determined in the Hydrochlorothiazide-Captisol inclusion complex in different ratios (1:1, 1:2 & 1:3) .Saturated solutions in 7.4 pH phosphate buffer were prepared by adding an excess amount of Hydrochlorothiazide containing complex and rotated for 48 h at 100 RPM to reach equilibrium at 25°C using an orbital shaker. The filtered supernatants were further diluted if necessary with 7.4 pH phosphate buffer and analyzed spectrophotometrically using a UV/visible spectrophotometer (Shimadzu UV-1650 PC (E) 230 V, Tokyo, Japan at 272 nm). The solubility of Hydrochlorothiazide was calculated using the Hydrochlorothiazide calibration.



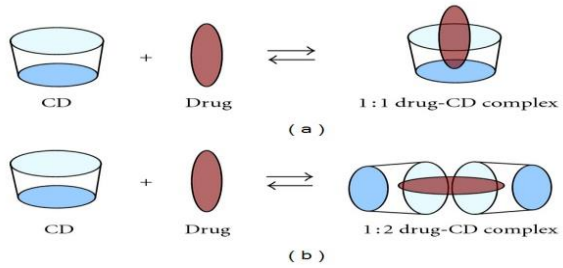
Hydrochlorothiazide-Captisol ratio

NOVEL HYBRIDIZATION TECHNIQUE

Novel hybridization technique was implemented by the combination approach of complexation with liquisolid technique. Here, a complex of Hydrochlorothiazide-captisol (1:1 molar ratio) is dispersed in the non-volatile solvent & then the carrier was added into mortar and pestle and mixed with it for 10 to 20 min. Then coating materials were completely mixed with the above mixture to form a free-flowing powder. This free-flowing powder is mixed with other excipients & compressed into tablets by using a tablet compression machine using the same components. Formulation of Hydrochlorothiazide by novel hybridization technique will be optimized using 3^2 full factorial design.

COMPLEXATION METHOD:

Hydrochlorothiazide & captisol (Drug: βCD) inclusion complex was prepared in 1:1 molar ratio by using the co-solvents evaporation method. Hydrochlorothiazide was dissolved into ethanol (80%), while Captisol is dissolved into water (20%). The resulting solution was evaporated at 45 °C and the dried complex is passed through sieve no.44. Powdered Complex is compressed into a tablet by direct compression method by using Avicel pH 101 as a diluent, pregelatinized starch as a disintegrating agent and magnesium stearate and talc as a lubricant.



LIQUISOLID TECHNIQUE:

The liquisolid formulation was obtained by mixing the drug with non-volatile solvent and then the drug solution was mixed with carrier excipients where coating of the drug molecule with thin film is formed. The resulting liquid medication–carrier system was adsorbed on a coating agent to get a dry, free-flowing and nonadherent powder that can be easily compacted into tablets. So screening of non-volatile solvents, carrier and coating material was essential.

Screening of non-volatile solvents:

For screening, various non-volatile solvents such as Tween 20, Tween 40, Tween 60, Tween 80, Tween 85, Polyethylene glycol 200, Polyethylene glycol 400, Polyethylene glycol 600 is selected and excess quantity of drug and inclusion complex were added into it. These suspensions were kept for 48 hrs on an orbital shaker at room temperature and then filtered & analysed for best non-volatile solvent .

Screening of carrier and coating materials:

Carrier & coating material selection were based on liquid load factor and flowable liquid retention potential. The flowable liquid retention potential (Φ-value) of a powder means maximum amount of a non-volatile liquid retained inside powder bulk to maintain adequate flowability. The liquid load factor (Lf) is the mass ratio of the liquid medication to the carrier powder in the liquisolid formulation (W/W). To calculate Lf, non-volatile solvent was dropwise added to 10 g carrier powder followed by blending for 1 min and carrier powder was evaluated for flowability . Lf and Φ-value were determined by,

Lf = Φ carrier + Φ coating (1/R) .

Φ value = weight of liquid medication / weight of powder

to find out the best suitable carrier and coating material ratios .

FORMULATION OF LIQUISOLID TABLETS

10 mg of Hydrochlorothiazide drug was solubilised in three different non volatile solvent systems (PG, PEG 400, Tween 80) with different drug: vehicle ratio (1:0.5, 1:1, 1:2, 1:3). Then required amount of carrier material (Avicel PH 102) was added to the above liquid by continous mixing for a period of 10 to 20 minutes in a mortar. Then coating material (Aerosil 200) was added to the above mixture and mixed it thoroughly.

Then to the above mixture 5% disintegrant (sodium starch glycolate) and glidant (talc) were added and mixed. The final mixture was compressed into tablet by direct compression.

CHARACTERIZATION OF FORMULATION:

DIFFERENTIAL SCANNING CALORIMETRY (DSC)

DSC is a method for the detectection of any physicochemical interaction between drug and excipients and it was done. The pure drug, hydrochlorohiazide : Captisol inclusion complex and the optimized formulation were subjected to thermal analysis using a differential scanning calorimeter for drug-excipient compatibility study over a temperature range of 0 °C–450 °C with a heating rate of 10 °C/min. The atmosphere around the sample cell was purged with nitrogen 200 mL/min. 4.0–6.0 mg sample amount was used for DSC testing. The instrument was calibrated by using indium and zinc as a standard and empty pan was used as a reference.

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

FTIR spectroscopy helps in the determination of any kind of chemical interactions among drug and excipients used in the formulation and study was done as outside analysis at Dharmsinh Desai University, Nadiad, Gujarat, India. The FTIR spectra of pure drug, Hydrochlorothiazide:captisol inclusion complex and optimized formulation were obtained in the frequency range of 4000–500 cm^{-1} and resolution of 4 cm^{-1}.

X-RAY DIFFRACTION (XRD)

For the identification of crystalline structure after complexation, the XRD study of the pure drug and Hydrochlorothiazide: Captisol inclusion complex was carried out as outside analysis at Dharmsinh Desai University, Nadiad, Gujarat, India with Cu- target X-ray tube and detector.

EVALUATION OF POWDER BLEND:

Materials & Methodology:

Preformulation study is the characterization of the physiochemical parameters of the drug substance by the application of biopharmaceutical principles with the goal of designing an optimum drug delivery system. The characterisation of drug and the drug-excipient compatibility information decides most of the subsequent events and approaches in development of the formulation. Preformulation study involves the physiochemical characterization of the drug, solubility determination of the drug. determination of the drug-excipient compatibility, development of the analytical methods and the stability studies.

The prepared powder blend were subjected to evaluation as per the methods suggested in the Indian Pharmacopoeia like angle of repose, bulk density, tap density, compressibility index, Hausner's ratio.

a. Angle of repose

The angle of repose is the maximum angle which is formed between the surface of a pile of powder and horizontal surface. It is determined by the funnel method. A funnel was kept vertically at a specified height and the funnel bottom was closed. 10 gm of

sample was filled inside the funnel. Then funnel was opened to release the powder to form a smooth conical heap which just touches the tip of the funnel. From the powder cone, the radius of the heap (b) were measured. The angle of repose is represented us and is calculated:

b. Bulk density

The bulk densities of the samples were determined by transferring the accurately weighed sample of powder to the graduated 50 ml measuring cylinder .The initial volume (bulk volume)and weight was noted.

c. Tapped density

An accurately weighed powder sample was transferred to the graduated 50 ml measuring cylinder and was placed on the tap density apparatus. The apparatus was operated for a fixed number of taps. The final volume (tap volume) of the tapped mass. was noted.

d. Hausner's ratio:

Hausner's ratio is the ratio of the initial volume of the powder mass to the final volume of the powder mass obtained after specified number of tapping.

e. Compressibility:

The compressibility index is determined from the tap volume and bulk volume. The basic method used for the determination of compressibility index is to measure the bulk volume and the final tapped volume after a fixed number of tapping until no change in volume occurs. It is represented in percentage.

EVALUATION OF TABLETS:

a. Weight variation test

20 tablets were selected at random and weighed individually. The average weight of each batch of tablet was calculated. Individual weights of the tablets were compared with the average weight. Since the tablet weighed around 250mg, IP specifies that the tablets pass the test if not more than two of the individual weights deviate from the average weight by more than 7.5%.

b. Friability

This was performed to evaluate the ability of tablet to withstand abrasions. Ten tablets were weighed and placed in the tumbling chamber of Roche friabilator which rotated for 100 revolutions at a speed of 25 rpm. The tablets were again weighed and the loss in weight. Friability value should not exceed 1% according to IP specification.

c. Hardness

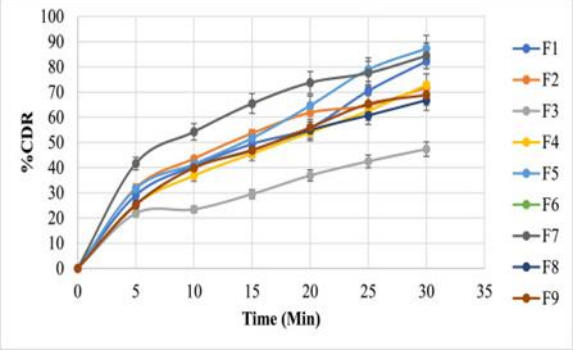
Hardness of the tablet was measured by Pfizer tablet hardness tester. The reading was noted from the needle of pressure dial which may be expressed in kilograms/

d. Assay of tablet

Ten tablets were randomly weighed and crushed. Calculated the average weight and taken the powder equivalent to 10 mg of Hydrochlorothiazide base in a 100 ml volumetric flask. Add few ml methanol and sonicated for 10 minute. Then volume made up to 100 ml with 0.05M phosphate buffer pH 7.4. Then 1ml of resultant solution diluted in 100ml with 0.05M acetate buffer pH 4.5 and the absorbance was measured using UV spectrophotometer at 274nm.

f. In-vitro Dissolution studies

The Hydrochlorothiazide release from different formulations was determined using a USP XXIII paddle apparatus 2 under sink condition. The dissolution medium was 300ml 0.05M phosphate buffer pH 7.4 at 37 0.5 °C; at 50 rpm, to simulate in vivo conditions. The formulation prepared was subjected to dissolution tests for 45 minutes, Sample (10 ml) was withdrawn at predetermined time intervals, filtered through Whattman filter paper and replaced by an equal volume of dissolution medium. Drug content in the dissolution sample was determined by UV spectrophotometer at 232nm. The result revealed that F5 showed the highest drug release among all batches within 30 min .



EVALUATION OF PHYSICOCHEMICAL CHARACTERISTICS OF HYDROCHLOROTHIAZIDE FORMULATION

Disintegration test

The disintegration test was carried out in 7.4 pH phosphate buffer at 37°C ± 0.5°C and the time taken for the disintegration of tablets were noted. Experiments were performed in triplicate .

Dissolution studies

USP dissolution test apparatus type II (Paddle) was used for dissolution studies. A dissolution test was carried out using 900 ml of phosphate buffer 7.4 pH at 37 ± 0.5°C temperature and 75 RPM. 5 ml sample solutions were collected at a precise time interval of 5, 10, 15, 20, 25, and 30 min and an equivalent volume of fresh solution was added to maintain the sink condition. The sample solution was analysed at 272 nm using a spectrophotometer against a suitable blank.

COMPARISON OF DISSOLUTION PROFILE WITH MARKETED PRODUCT:

A comparison of the dissolution profile of the Hydrochlorothiazide formulation of Novel hybridization technique with the pure drug, marketed formulation (hydrochlorothiazide), tablets prepared by complexation and liquisolid techniques was carried out as per dissolution studies.

Stability studies

The formulation was subjected to stability study at 40° ± 2 °C and 75 ± 5% RH conditions for 1 month to evaluate storage condition. After 10, 20 and 30 days the formulation it is analysed for content uniformity and dissolution rate as per the procedures reported.

CONCLUSION

The work done for solubility enhancement of Hydrochlorothiazide by novel hybridization technique showed its ability with appreciable the dissolution study showed that the formulations of novel hybridization techniques exhibited higher solubility and dissolution as compared to a pure drug, marketed formulation, complexation and liquisolid techniques. Based on the results, it can be concluded that novel formulation will give immediate drug release with reduced dose frequency.

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