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Formulation Development And Evaluation Of Sustained Release Tablets Of Cinnarizine

K.SATHISH KUMAR, Mohmed Fazal Ul-Haq, Dr. Dr. M.Sunitha Reddy, Dr. S. Shobha Rani,
Centre for Pharmaceutical Sciences, IST, JNTUH

1. INTRODUCTION:

1.1 MODIFIED DRUG DELIVERY SYSTEM:

Modified release (MR) dosage forms are a type of dosage forms developed by altering drug absorption or the site of drug release in order to achieve predetermined clinical observations. The therapeutic usefulness of modified release product include improve the drug efficacy and decreases the drug adverse effects, increased convenience and patient compliance, optimized performance, a greater selectivity towards the specific receptor or specific site, or new indications.

According to the US Food and Drug Administration (US FDA), MR solid oral dosage forms include extended-release (ER) and delayed-release (DR) products. A DR dosage form releases the drug (or drugs) at a time other than immediately following administration. An ER dosage form is formulated to make the drug available over an extended period after drug administration, thus allowing a reduction in dosing period compared to a drug presented in a conventional dosage form (e.g., a solution or an immediate release [IR] dosage form). For oral applications, the term "extended release" is usually interchangeable with "sustained release," "prolonged release," or "controlled release."

The objective of modifying oral drug release is to modulate the rate of drug input (i.e., dissolution or absorption) in the intestinal tract to achieve a predefined plasma profile. Common modes of drug release include delayed release (e.g., using an enteric coating), site-specific or timed release (e.g., for colonic delivery), extended release (e.g., zero-order, first order, etc.), or programmed release (e.g., pulsatile, etc.)

1.2 SUSTAINED BLOOD LEVEL

The size and frequency of dosing is determined by pharmacodynamic and pharmacokinetic properties of a drug. The slower the rate of absorption, the lower the blood concentration fluctuates

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in a dosing interval. This enables high dose will give less frequently. For drugs with shorter half-life the use of extended release product may maintain therapeutic concentration for a prolonged period.

In the controlled release dosage forms plasma drug concentration is maintained when compared to conventional dosage forms

1.3 CINNARIZINE

Cinnarizine is a pipprzine derivative it is mainly used as Anti-histamanic drug. this was first synthesized by Janssen Pharmaceuticals in 1955, cinnarizine is an anti-histaminic drug mainly used for the control of vestibular disorders and motion sickness. Cinnarizine is a specific Ca^{+2} channel blocker that mainlywork on the central vestibular system to interfere with the signal transmission between vestibular apparatus of the inner ear and the vomiting center of the hypothalamus.

1.4 USES OF CINNARIZINE

In convention uses have cinnarazine have some serious adverse effect and also the absorption of cinnarazine depends on the P^H of gastric fluids. Poor solubility of cinnarizine causing poor dissolution in gastrointestinal (GI) tract is the major problem for drugs meant for systemic action after oral administration, like cinnarizine. Currently available of cinnarizine are commercialized globally as immediate release preparations presenting low absorption with low and erratic bioavailability. In this present study we are developing the new formulation *i.e.* sustains release of cinnarizine tablets.

Modified release (MR) dosage forms are a type of dosage forms developed by altering drug absorption or the site of drug release in order to achieve predetermined clinical observations The therapeutic usefulness of modified release product include improve the drug efficacy and decreases the drug adverse effects, increased convenience and patient compliance, optimized performance, a greater selectivity towards the specific receptor or specific site, or new indications.

2. LITARATURE REVIEW

Previously cinnarizine has developed some other dosage forms or novel drug delivery system which are used to improve the bioavailability and solubility of cinnarizine

FAST DISSOLVING TABLETS:

The fast disolving tablets of cinnarizine could serve as suitable tablet for fast dissolving of cinnarazine dablets in ganstro intastinal can improve the solubility and bioavailability of cinnarizine.

The fast release tablets of cinnarizine which improve the dissolution of cinnarizine in In-vitro(80-90%,60min) comparied with drug alone it is less then 50% in 80 minuts because of the higherhydrophilic character imparted by hydrophilic carriers and reduction in drug crystallinity in

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case of granules. Use of fluidized hot melt granulation method which means prepared with PEG 600 as a melt binder, which no need requirement of solvents or water. Another use of excipient i.e. chitosan it is a disintegrate the main to improve the solubility with this we can achieve the disarble bioavailability of cinnarizine.

Other methods of preparing the fast dissolving tablet of cinnarizine is

Combination of super disintegrates sodium starch glycol ate (SSG) and croscarmellose sodium (CCS) and camphor as a subliming material. The aim of camphor adding is aid the porosity of tablet. Normally used formula is (SSG = 12mg, CCS = 12mg, and camphor = 10mg).when compared to widely used commercial tablet was reported to be more effective with drug release of 99% in 16min.

3. FORMULATION DEVELOPMENT

3.1 Direct compression method:

- This technique will affect compression of drugs at relatively low filler to drug ratio, with little addition of preparatory techniques.
- Materials used as dry binders should possess adequate cohesive or compressibility properties in order to form satisfactory tablets of acceptable hardness and friability.
- They should possess adequate flow ability and bulk density to ensure the die cavities are uniformly filled and hence tablets of uniform weight and drug content would be obtained.
- They should also have high capacity or low binder to drug ratio in order to make possible the manufacture of suitable sized tablets containing relatively high doses of drugs.

3.2 Advantages

- Direct compression method requires fewer processing steps (unit operations) and less equipment. Therefore, the method is potentially less expensive than other methods used in tablet manufacture.
- Tablet manufacture can be carried out without the involvement of moisture and heat. Hence, product stability is almost guaranteed.
- Some direct compressible excipients possess inherent disintegration properties e.g., microcrystalline cellulose.
- Changes in dissolution profile are less likely to occur in tablets manufactured by direct compression (if stored for a long time) than in those prepared by wet granulation.

3.3 Disadvantages

- There are a number of reasons why direct compression may not be suitable for a wide array

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of products and they include:

- High-dose drugs may present problems with direct compression if it is not easily compressible by itself
- The choice of excipients used in the manufacture of tablets by direct compression technology is highly restricted since most materials do not have inherent binding properties.

4.RESULTS AND DISCUSSION:

Tests for identification:

Physical appearance:

Cinnarizine was found to be aswhite powder.

Melting point:

Melting point of Cinnarizine was determined by capillary tube method and it was found to be melting at117-121℃

Determination of Absorption Maximum (λ_{max}):

UV-Spectrophotometric method was used for estimation of cinnarizine .The λ_{max} of cinnarizine (10 µg/ml) in 0.1 N HCl was scanned in UV-Visible Spectrophotometer in the wave length of 200 – 400 nm

Standard graph of cinnarizine in 0.1N HCl by UV-spectrophotometer at λ_{max} 250nm

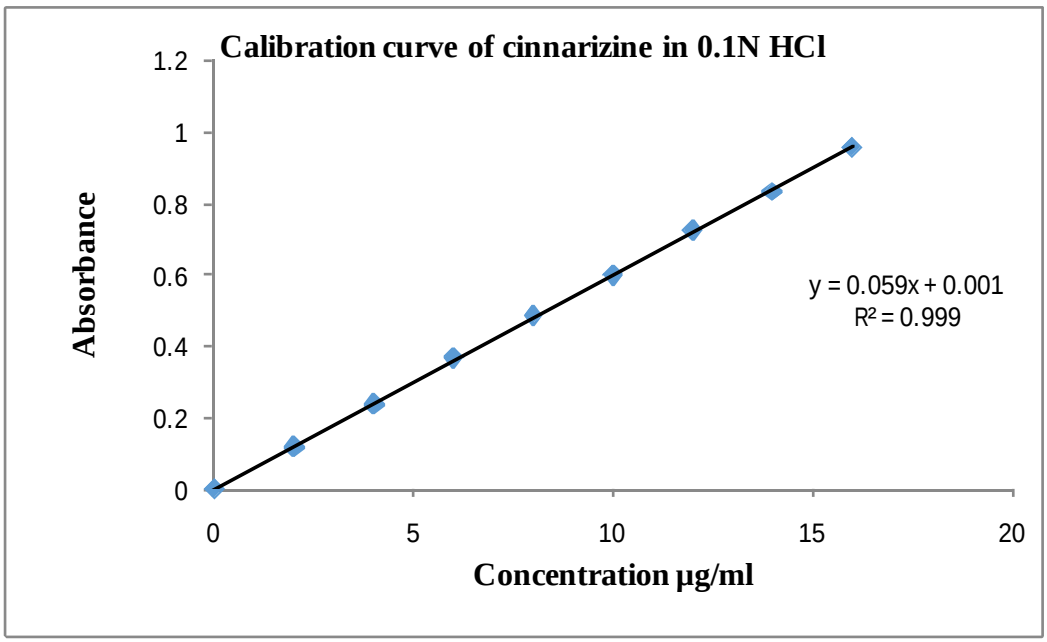

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Figure 1: Calibration curve of cinnarizine in 0.1N HCl

Standard graph of Cinnarizine in pH 6.8 phosphate buffer at λ_{max} 250nm

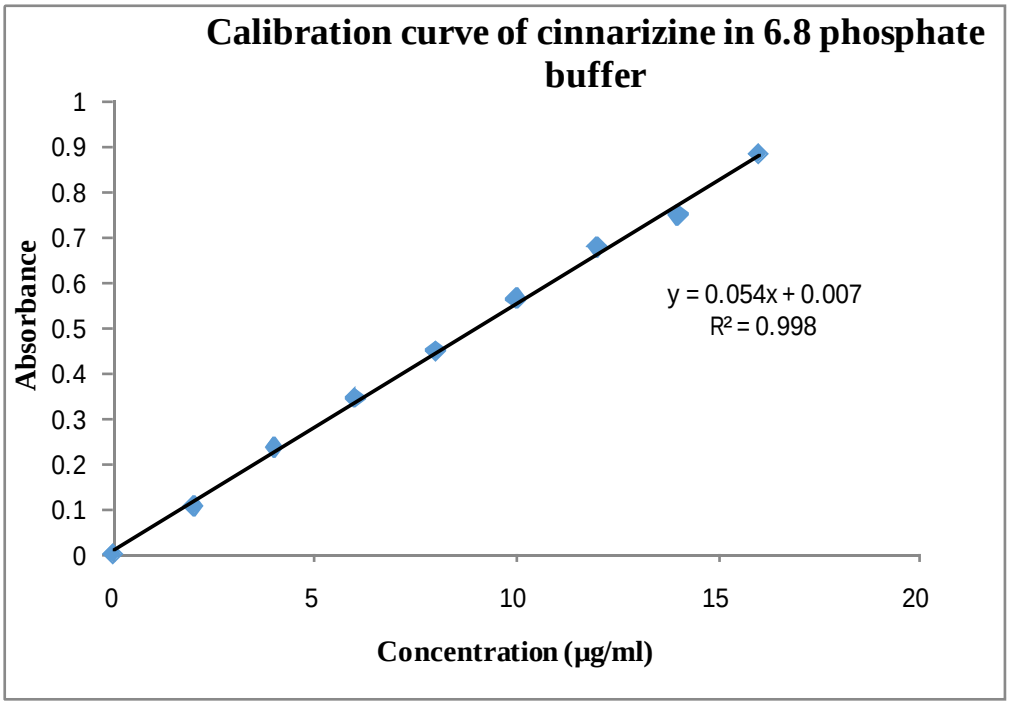

Figure 2: Calibration curve of cinnarizine in 6.8 phosphate buffer

SOLUBILITY PROFILE OF CINNARIZINE

Cinnarizine was found to be insoluble in water. Cinnarizine exhibits poor aqueous and pH-dependent solubility. With increase in pH, solubility of Cinnarizine decreases.

DRUG- EXCIPIENT COMPATIBILITY STUDIES

Fourier Transform Infrared (FTIR) Spectroscopy

The Fourier Transform Infrared (FTIR) Spectrum was recorded with FT-IR Perkin Elmer spectrometer in KBr dispersion in the range of 400-4000 cm^{-1}. The spectrum was helpul to know any possible chemical interaction between drug and excipients.

PHYSICAL PROPERTIES OF PREPARED POWDER BLEND

The physical properties like Bulk density, Tapped density, Compressibility index (CI), Angle of repose and Hausner's ratio were calculated and tabulated.

The results of the physical test of all the formulations were within the limits and complied with the standards and indicate good floe properties.

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EVALUATION OF PHISICAL PARAMETERS OF SUSTAINED RELEASE TABLETS OF CINNARIZINE

All the prepared formulation tested for physical parameters like weight variation, hardness, thickness, friability, Raft volume, Raft weight and Raft strength were found to be within the pharmacopeial limits. The drug content (assay) of all the formulations was determined and was found to be within the permissible limits. This study indicated that all the prepared formulations were good

IN VITRO DRUG RELEASE STUDIES OF PREPARED FORMULATION

The cumulative percentage of drug release from formulation F1,F2,F3,F4,F5,F6,F7,F8 and F9 was 96.95±1.03,98.18±1.5,96.43±0.7,94.71±1.8,95.58±1.4,97.45±0.8,96.5±1.30,88.39±2.4 in 12 hours.

All these five formulations (F1. F2, F3, F4,F5,F6,F7,F8 and F9) floated with lag time of less than 1 minute. Formulation F3 considered as best formulation among all, because of its controlled drug release drug release and kinetic release profiles. This formulation follows zero order kinetics.

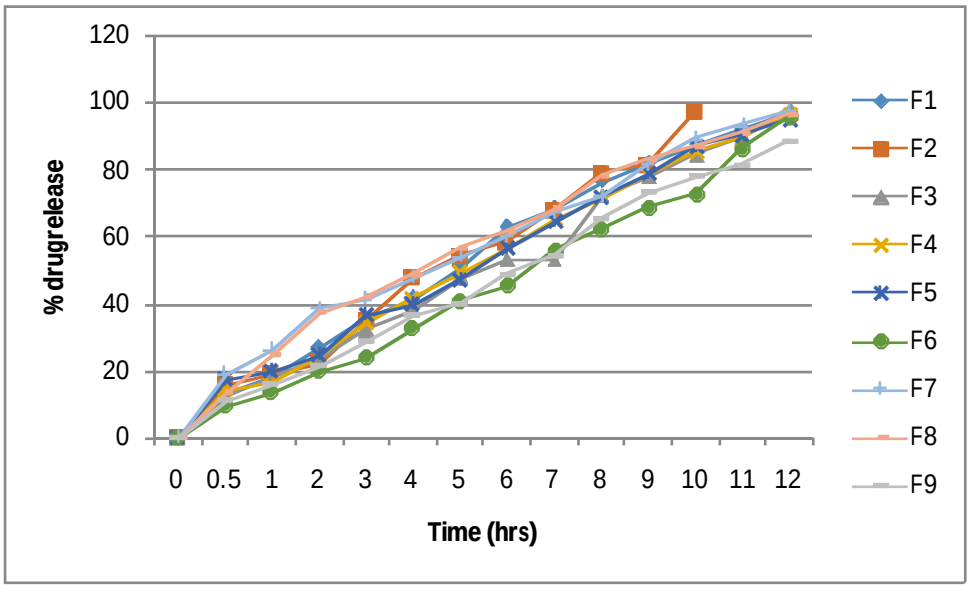

Figure 3: Cumulative percentage drug release profiles of formulations

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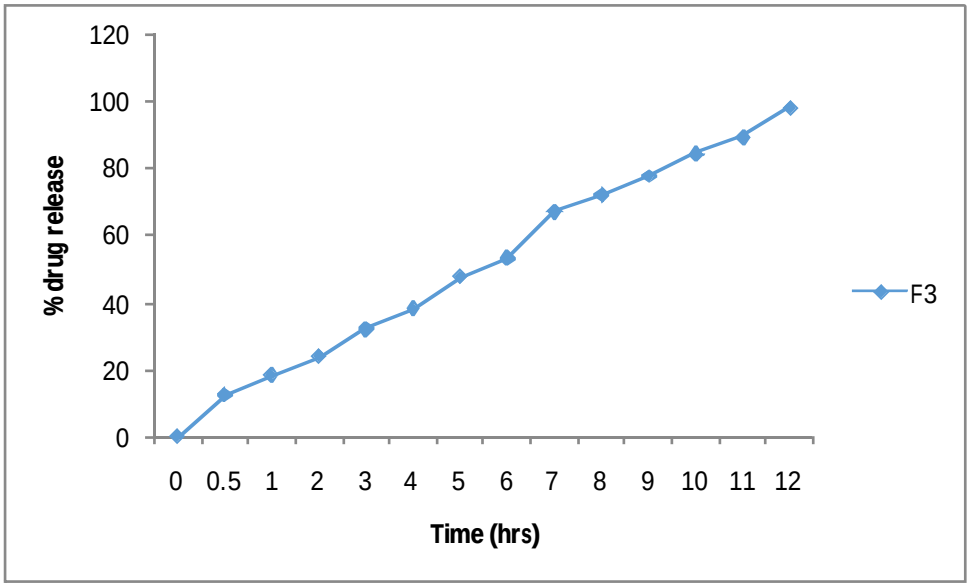

Figure 4: Cumulative drug release curve of F3

Accelerated stability studies were performed at a temperature of 40 ± 2°C, 75 ± 5% RH a period of three months (90 days) on the promising sustained release tablets which were shows there were no changes in the colour, integrity and no significant changes in the drug content and *in vitro* release.

5. CONCLUSION

The sustained release cinnarizine tablets ware prepared by direct compression method. The nature of the polymers influences the physical and release characteristics of the tablet. The semi-synthetic and synthetic polymers like HPMC, Eudragit and Carbopol were used for sustain release of the drug with the pre and post compression parameters, Eudragit and Carbopol with Hydroxy propyl methyl cellulose and lactose mono hydrate as a diluent was optimized (F3), leads to sustained release of drug from matrix tablet.

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