ABSTRACT

Candesartan cilexetil is a prodrug of candesartan – a compound that inhibits binding of angiotensin II to the AT₁ receptor. It is mainly used in the treatment of hypertension. In the present work attempts were made to prepare fast dissolving tablets of candesartan cilexetil by sublimation technique. The prepared formulations were evaluated for pre-compressional and post-compressional parameters. The compatibility of drug with other ingredients was checked by FTIR studies, these results revealed that there was no interaction between drug and other excipients. The values of pre-compressional parameters were within prescribed limits and indicated good free flowing properties. In all the formulations the hardness test indicates good mechanical strength. Friability of all formulations was less than 1. Drug content was found to be high (≥ 100.27%) and uniform in all the formulations. The tablet thickness was found to be 3.14 – 3.47. The weight variation results revealed that average percentage deviation was less then ± 7.5 %, which provides good uniformity in all formulations. The disintegration time of the tablets decreased significantly with increase in the concentration of subliming agent. The formulations CSC₃, CSM₃, CSA₃, and CSU₅ 50 % of drug released in 1.38, 2.55, 4.00 and 3.57 min, and 90 % of drug released in 3.39, 6.04, 7.50 and 7.18 min. The formulation CS (control) released 42.16 % in 60 min. Stability study carried out as per ICH guidelines for three months and results revealed that upon storage disintegration time of tablets decreased significantly (p<0.05). The results concluded that by adopting a systemic formulation approach, an optimum point could be reached in the shortest time with minimum efforts. Sublimation technique would be an effective alternative approach compared with the use of more expensive adjuvants in the formulations of fast dissolving tablets.

Keywords: Candesartan cilexetil, Fast dissolving tablets, sublimation technique, Croscarmilloose Sodium.

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INTRODUCTION

Now a day fast dissolving tablets are gaining more importance in the market. Currently these tablets are available in the market for treating many disease conditions. More is concerned on hypertension, migraine, dysphasia, nausea and vomiting, Parkinson’s disease, schizophrenia, pediatric emergency\(^1\)-\(^7\). These conditions are those which require the drug to be formulated as fast dissolving tablets. Some patient prefers fast dissolving tablets to conventional tablets best of ease of administration, swallowing, pleasant taste and availability in several flavors\(^8\).

The paediatric and geriatric patients are of particular concern. To overcome this, dispersible tablets\(^9\) and fast-disintegrating tablets\(^10\) have been developed. Most commonly used methods to prepare these tablets are; freeze-drying/lyophilization\(^11\) tablet molding\(^12\) and direct-compression methods\(^13\). Lyophilized tablets show a very porous structure, which causes quick penetration of saliva in to the pores when placed in oral cavity\(^14\). The main disadvantages of tablets produced are, in addition to the cost intensive production process, a lack of physical resistance in standard blister packs and their limited ability to incorporate higher concentrations of active drug. Molded tablets dissolve completely and rapidly. However, lack of strength and taste masking are of great concern\(^15\). Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets\(^16\).

The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation and solid dispersion)\(^17\). The dissolution of drug can also be influenced by disintegration time of the tablet. Faster disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and faster dissolution\(^18\).

Candesartan cilexetil is chemically 2-Ethoxy-3-[21-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] - 3Hbenzoimidazole- 4-carboxylic acid 1- cyclohexyloxy carbonyloxy ethyl ester.\(^19\) Candesartan cilexetil is a prodrug of Candesartan – a compound that inhibits binding of angiotensin II to the AT\(_1\) – receptor. Candesartan cilexetil is hydrolyzed to candesartan during absorption from the gastrointestinal tract\(^20\) It is mainly used in the treatment of hypertension. The typical dose of Candesartan cilexetil is 16 mg per day in patients who are not volume depleted. It may be given once or twice daily with total daily doses ranging from 8 mg to 32 mg\(^21\).

In the present study, an attempt was made to develop fast dissolving tablets of candesartan cilexetil by sublimation technique to improve its bioavailability.

MATERIALS AND METHOD

Candesartan cilexetil was gift sample from Hetero Labs. Ltd. Medak district. (AP).
crosscarmellose sodium, camphor, urea, ammonium bicarbonate, menthol, mannitol, microcrystalline cellulose, talc, magnesium stearate, and all the other chemicals used were of pharmaceutical grade.

**Fourier transform infrared (FTIR) spectroscopy**

Compatibility studies were carried out to know the possible interactions between Candesartan cilexetil and excipients used in the formulation. Physical mixtures of drug and excipients were prepared to study the compatibility. Drug polymer compatibility studies were carried out using FTIR spectroscopy. IR spectrum of pure drug and excipients was seen in between 500-4000 cm⁻¹ and are shown in Figure 1.

**Preparation of tablet**

Candesartan cilexetil 4 mg was taken and mixed with mannitol, directly compressible microcrystalline cellulose, super disintegrant and camphor (3%, 6%, 9%) in plastic container. Magnesium stearate and talc were passed through sieve No. 60 and blended with initial mixture in the plastic container followed by direct compression of blend (Table 1). After compression the tablets were collected and vacuum dried at 60°C until the constant weight is obtained to ensure the complete removal of sublimable component to make a tablet porous.

**Evaluation of tablets**

Tablet was evaluated for hardness, friability, weight variation, thickness, disintegration time, wetting time, water absorption ratio, drug content and stability study. The Pfizer hardness tester and Roche friabilator were used to test hardness and friability loss respectively. In weight variation test, 20 tablets were selected at random and average weight was determined using electronic balance. Tablets were weighed individually and compared with average weight. Disintegration time was determined using USP Tablet disintegration test apparatus using 900 ml distilled water at room temperature. Thickness of tablets was determined by using dial caliper, wetting time study, a piece of tissue paper folded twice was kept in culture dish containing 6 ml of distilled water. A tablet having small amount of amaranth powder on upper surface was kept on tissue paper. A time required to develop a red color on upper surface of tablet was recorded as the wetting time. For drug content analysis, a total 10 tablets were weighed and powdered. The powder equivalent to 4 mg of candesartan cilexetil was taken and dissolved in phosphate buffer 6.8. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically at 255 nm. Using 900 ml of buffer monitored *in-vitro* dissolution of candesartan cilexetil from tablets at 37±0.5°C at 50 rpm using programmable dissolution tester. Aliquots were withdrawn at 1 min time intervals. Aliquots, following suitable dilution were assayed spectrophotometrically at 255 nm. The stability study of
the tablets were carried out according to ICH guidelines by storing tablets in stability chamber at 40±2\(^{0}\)C/75±5% RH for 3 months

RESULTS AND DISCUSSION

Science, the flow properties of the powder mixture are important for the uniformity of mass of tablets, the flow of powder mixture was before compression of tablets. The values of pre-compressional parameters were within prescribed limit as per USP XXVII and indicate good flow properties. The results are shown in table 2. The post compressional parameters results are shown in table 3and 4. In all the formulations the hardness test indicate good mechanical strength. The hardness of tablet decrease with increase in amount of sublimable component. Friability of all formulation was less than 1%, which indicates the tablets had good mechanical resistance. Drug content was found to be high (≥100.27 %) and uniform in all formulations. The tablet thickness was found to be 3.14 to 3.47. The weight variation results revealed that average percentage deviation of 20 tablets of each formula was less than ± 7.5%, which provide good uniformity in all formulations. The disintegration time of decreased significantly with increase in concentration of subliming agent. The tablets prepared by sublimation technique rapidly exhibit high pores and disintegrate the tablets rapidly. It may be due to their lowest hardness and maximum pores structure was responsible for faster water uptake; hence it facilitates wicking action of crasscarmellose sodium in bringing about faster disintegration. Wetting time of tablets was decreased with increase in the concentration of the subliming agent. Wetting time is closely related to the inner structure of the tablet. The wetting time of all formulations were found to be in the range of 65 to 148 sec. The dissolution profiles of all formulations are shown in Figure 2 to 5. Out of seven formulations, the formulations prepared by using camphor as subliming agent show faster drug release within 4 to 7 min. in-vitro profile of candesartan cilexetil shown in Figure 6 and in Table 5. The \( t_{50\%} \) and \( t_{90\%} \) values changed with changing concentration of subliming agent. The formulation CSC\(_1\), CSC\(_2\) and CSC\(_3\) shows faster drug release. The formulations CSC\(_3\), CSM\(_3\), CSA\(_3\), and CSU\(_3\) 50 \% of drug released in 1.38, 2.55, 4.00 and 3.57 min, and 90 \% of drug released in 3.39, 6.04, 7.50 and 7.18 min. The formulation CS (control) released 42.16 \% in 60 min.

The stability studies results revealed that, the disintegration time, wetting time was decreased significantly (Table 6). During the sublimation procedure all the formulations were kept in vacuum dryer at 45\(^{0}\)C for 60 min. at this time sum amount of subliming agent may be left in the formulations after vacuum drying. But in case of stability study, the selected formulations were
kept at 40°C for 90 days. This extended exposure time may lead to evaporation of subliming agent, which may be left after sublimation techniques leads to increased formation of pores in the tablets. So, the disintegration and wetting time of tablets were decreased after stability study.

Conclusion

It may be concluded that by adopting a systemic formulation approach, an optimum point could be reached in the shortest time with minimum efforts. Sublimation technique would be an effective alternative approach compared with the use of more expensive adjuvants in the formulations of fast dissolving tablets.

Table 1: Formulation of Candesartan Cilexetil FDT

| Ingredients                  | Formulation Code |
|------------------------------|------------------|
| Candesartan cilexetil        | CS               |
| Mannitol                     | 4                |
| CCS                          | 94               |
| Camphor                      | --               |
| Ammonium bicarbonate         | --               |
| Menthol                      | --               |
| Urea                         | --               |
| Talc                         | 1                |
| Magnesium stearate           | 1                |
| Total wt (mg)                | 100              |

| Ingredients                  | Formulation Code |
|------------------------------|------------------|
| Candesartan cilexetil        | CSC1             |
| Mannitol                     | 85               |
| CCS                          | 6                |
| Camphor                      | 3                |
| Ammonium bicarbonate         | --               |
| Menthol                      | --               |
| Urea                         | --               |
| Talc                         | 1                |
| Magnesium stearate           | 1                |
| Total wt (mg)                | 100              |

Table 2: Precompressional Parameters Of Candesartan Cilexetil FDT

| Formulation code | Angle of repose* (degree) ±SD | Bulk density* (g/cc) ± SD | Tapped density* (g/cc) ± SD | Carr’s index* (%) ± SD | Hausner’s Ratio* ± SD |
|------------------|-------------------------------|--------------------------|-----------------------------|------------------------|-----------------------|
| CS               | 32.43 ± 1.37                 | 0.50 ± 0.06              | 0.61 ± 0.02                 | 18.43 ± 1              | 1.22 ± 0.02           |
| CSC1             | 29.14 ± 1.08                 | 0.49 ± 0.06              | 0.60 ± 0.01                 | 17.80 ± 1.23           | 1.21 ± 0.03           |
| CSC2             | 30.30 ± 1.17                 | 0.51 ± 0.06              | 0.61 ± 0.01                 | 17.68 ± 1.02           | 1.21 ± 0.02           |
| CSC3             | 26.37 ± 1.26                 | 0.52 ± 0.06              | 0.63 ± 0.01                 | 21.05 ± 1.03           | 1.21 ± 0.03           |
| CSM1             | 28.50 ± 1.20                 | 0.52 ± 0.06              | 0.63 ± 0.02                 | 16.87 ± 1.25           | 1.25 ± 0.03           |
| CSM2             | 27.21 ± 1.41                 | 0.52 ± 0.06              | 0.62 ± 0.01                 | 15.88 ± 1.36           | 1.18 ± 0.03           |
| CSM3             | 29.11 ± 1.45                 | 0.51 ± 0.06              | 0.62 ± 0.02                 | 16.85 ± 1.29           | 1.20 ± 0.03           |
| CSA1             | 30.19 ± 1.27                 | 0.53 ± 0.06              | 0.62 ± 0.01                 | 15.08 ± 1.89           | 1.17 ± 0.03           |
| CSA2             | 27.52 ± 1.33                 | 0.48 ± 0.06              | 0.60 ± 0.02                 | 20.03 ± 1.56           | 1.25 ± 0.03           |
| CSA3             | 28.73 ± 1.23                 | 0.52 ± 0.06              | 0.63 ± 0.02                 | 17.77 ± 1.57           | 1.21 ± 0.02           |
| CSU1             | 29.86 ± 1.46                 | 0.48 ± 0.06              | 0.60 ± 0.01                 | 19.86 ± 1.49           | 1.24 ± 0.03           |
| CSU2             | 27.12 ± 1.56                 | 0.51 ± 0.06              | 0.60 ± 0.01                 | 14.80 ± 1.69           | 1.17 ± 0.03           |
| CSU3             | 29.09 ± 1.01                 | 0.50 ± 0.06              | 0.61 ± 0.01                 | 17.82 ± 1.75           | 1.21 ± 0.03           |
* Average of three determinations

Table 3: Post-Compressional Parameters of Candesartan Cilexetil FDT

| Formulation Code | Hardness* (Kg/cm²) ± SD | Thickness* (mm) ± SD | Friability (%) | Weight variation* (mg) ± SD |
|------------------|--------------------------|----------------------|----------------|-----------------------------|
| CS               | 2.5 ± 0.42               | 3.47 ± 0.08          | 0.48           | 102 ± 1.81                  |
| CSC1             | 3.1 ± 0.15               | 3.33 ± 0.20          | 0.26           | 100 ± 1.06                  |
| CSC2             | 3.0 ± 0.20               | 3.35 ± 0.28          | 0.29           | 97 ± 1.45                   |
| CSC3             | 2.5 ± 0.05               | 3.35 ± 0.14          | 0.31           | 98 ± 0.67                   |
| CSM1             | 2.2 ± 0.10               | 3.23 ± 0.19          | 0.57           | 102 ± 1.42                  |
| CSM2             | 2.1 ± 0.21               | 3.25 ± 0.09          | 0.53           | 98 ± 1.57                   |
| CSM3             | 2.0 ± 0.15               | 3.35 ± 0.12          | 0.41           | 100 ± 0.78                  |
| CSA1             | 2.5 ± 0.10               | 3.43 ± 0.15          | 0.63           | 97 ± 1.49                   |
| CSA2             | 2.1 ± 0.13               | 3.31 ± 0.17          | 0.73           | 98 ± 1.38                   |
| CSA3             | 2.0 ± 0.12               | 3.27 ± 0.10          | 0.77           | 101 ± 1.22                  |
| CSU1             | 3.0 ± 0.10               | 3.32 ± 0.25          | 0.30           | 100 ± 0.92                  |
| CSU2             | 2.5 ± 0.15               | 3.31 ± 0.15          | 0.67           | 101 ± 1.36                  |
| CSU3             | 2.0 ± 0.21               | 3.14 ± 0.21          | 0.65           | 101 ± 0.29                  |

* Average of three determinations

Table 4: In Vitro Disintegration Time, Wetting Time, Water Absorption Ratio and Drug Content Of Candesartan Cilexetil FDT

| Formulation Code | In vitro disintegration time* (sec) ± SD | Wetting time* (sec) ± SD | Water absorption ratio* ± SD | Drug Content* (%) ± SD |
|------------------|------------------------------------------|--------------------------|----------------------------|------------------------|
| CS               | 100 ± 1.23                               | 148 ± 1.03               | 68 ± 1.36                  | 98.96 ± 0.86           |
| CSC1             | 30 ± 1.36                                | 70 ± 1.53                | 82 ± 1.39                  | 99.92 ± 0.45           |
| CSC2             | 28 ± 2.36                                | 68 ± 1.37                | 83 ± 1.53                  | 100.27 ± 0.53          |
| CSC3             | 25 ± 1.56                                | 65 ± 1.25                | 84 ± 1.20                  | 99.17 ± 1.96           |
| CSM1             | 32 ± 1.53                                | 72 ± 1.23                | 82 ± 1.30                  | 98.18 ± 1.17           |
| CSM2             | 29 ± 1.28                                | 69 ± 1.35                | 83 ± 1.69                  | 99.62 ± 0.97           |
| CSM3             | 27 ± 1.59                                | 67 ± 1.54                | 84 ± 1.98                  | 98.83 ± 1.31           |
| CSA1             | 34 ± 1.46                                | 74 ± 2.03                | 82 ± 1.29                  | 99.15 ± 1.47           |
| CSA2             | 32 ± 1.44                                | 72 ± 2.45                | 83 ± 1.62                  | 98.93 ± 0.64           |
| CSA3             | 28 ± 1.29                                | 68 ± 2.09                | 85 ± 1.93                  | 99.12 ± 1.27           |
| CSU1             | 34 ± 1.34                                | 74 ± 2.56                | 80 ± 1.63                  | 99.03 ± 1.02           |
| CSU2             | 31 ± 2.31                                | 71 ± 0.29                | 82 ± 1.53                  | 99.13 ± 1.90           |
| CSU3             | 29 ± 2.04                                | 69 ± 2.26                | 83 ± 1.49                  | 98.54 ± 1.21           |

* Average of three determinations

Table 5: Release Profile Of Candesartan Cilexetil Fast Dissolving Tablets Prepared By Sublimation Method

| Formulation Code | t50%* | t90%* |
|------------------|-------|-------|
| CS               | --    | --    |
| CSC1             | 3.57 ± 0.12 | 6.18 ± 0.29 |
| CSC2             | 2.51 ± 0.21 | 5.15 ± 0.32 |
| CSC3             | 1.38 ± 0.39 | 3.39 ± 0.56 |
Table 6: Results of Stability Study

| Formulation Code | In vitro disintegration time* (sec) ± SD | Wetting time* (sec) ± SD | Drug Content* (%) ± SD |
|------------------|----------------------------------------|--------------------------|------------------------|
| CSC3             | 22 ± 1.03                              | 60 ± 1.65                | 99.14 ± 0.57           |
| CSM              | 24 ± 1.49                              | 62 ± 1.72                | 98.82 ± 0.79           |
| CSU3             | 27 ± 0.56                              | 64 ± 1.13                | 98.52 ± 1.28           |
| CSA3             | 26 ± 2.43                              | 63 ± 1.54                | 99.10 ± 0.81           |

* Average of three determinations

Figure 1: IR spectrum of Candesartan cilexetil
Figure 2: Dissolution profile of formulations CSC1-CSC3

Figure 3: Dissolution profile of formulations CSM1-CSM3

Figure 4: Dissolution profile of formulations CSA1-CSA3
Figure 5: Dissolution profile of formulations CSU$_1$-CSU$_3$

Figure 6: Comparison of release profile ($t_{50\%}$ and $t_{90\%}$) of different formulations

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