FORMULATION AND EVALUATION OF TELMISARTAN FAST DISSOLVING TABLETS USING JACK FRUIT SEED STARCH AS SUPERDISINTTEGRANT

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ABSTRACT

Objective: The main objective of the current study is to enhance the solubility of Biopharmaceutical Classification System (BCS) Class-II drug Telmisartan using jack fruit seed starch as super disintegrant which increases drug release.

Methods: Starches were extracted using alkali technique using sodium hydroxide at 0.1%, 0.25%, and 0.5% concentrations and water from Jack fruit seed powder. These starches were evaluated for various physiochemical and physicochemical tests. Fast dissolving tablets were prepared using Telmisartan, jack fruit seed starch and Croscarmellose sodium in various concentrations using wet granulation technique. Various pre and post-compression study parameters were evaluated along with in vitro dissolution studies, characterization studies like Fourier Transform Infra-Red spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM), X-Ray Diffraction (XRD) and accelerated stability studies.

Results: Phytochemical tests revealed the presence of only starch in all the extracts. The starch prepared from 0.1% sodium hydroxide (FJS2) showed best physicochemical properties. From in vitro dissolution studies, it was observed that formulations F5 and F11 containing 15% w/w of FJS2 and 15% w/w of croscarmellose sodium showed faster disintegration and increased dissolution rate compared with other formulations. FTIR and DSC studies showed that there were no major interactions among drug and excipients. XRD studies revealed the nature of formulations. Accelerated stability studies revealed the stability of tablets.

Conclusion: Thus, the tablets prepared using Jack fruit seed starch revealed the super disintegrant property of starch.

Keywords: Jack fruit, Fast dissolving tablets, Telmisartan, Croscarmellose sodium

INTRODUCTION

Oral route of drug delivery is widely preferred due to its ease of administration. It is unpalatable in case of geriatrics and children. In order to make it palatable, fast-dissolving tablets (FDTs) are formulated. When these tablets come in contact with saliva in the mouth, they disintegrate fast and releases drug [1]. Fast dissolving tablets are widely used due to patient compliance, rapid action, increased bioavailability and fast disintegration [2]. These are prepared by granulation method. Superdisintegrants are employed to formulate fast dissolving tablets. Some of the superdisintegrants are sodium starch glycolate, croscarmellose and polyvinyl pyrrolidone. Their action depends upon the concentration. They are mixed with tablet formulations to promote the breakup of tablet slugs into smaller fragments in an aqueous environment, which increases the surface area and promotes rapid drug release. It promotes moisture penetration and dispersion of tablet matrix [3].

Nowadays natural super disintegrants are preferred over synthetic forms, due to several advantages like a wide range of availability, cheaper cost, non-irritating and non-toxic nature. Several gums, starches and mucilages have super disintegrant nature. These are useful in enhancing the solubility of poorly water-soluble drugs. In BCS class-II and class-IV drugs show low solubility. Some recent studies proved the application of plant derivatives like mucilage of Plantago ovata, Aloe vera, Hibiscus rosasinenis and Lotus bean gum as super disintegrants in formulating several BCS class-II drugs [4]. BCS class-II drugs have less water solubility and high permeability.

Jack fruit (Artocarpus heterophyllus) which belongs to the family Fabaceae, grows in evergreen tropical climates of India, Africa and Australia. Fruits grow up to 6 meters length with many seeds. Their seeds have a thick and durable seed coat which is brownish in colour. It contains a fleshy white cotyledon. These are rich in starch contents [5]. Telmisartan, which is an anti-hyperlipidemic agent, is selected as a drug of choice for the present study based on its pharmacokinetic parameters. It is a statin which acts by inhibiting the hepatic enzyme β-hydroxy-β-methyl glutaryl coenzyme A (HMGCoA) reductase. This prevents the conversion of HMGCoA to mevalonate in cholesterol biosynthesis [6].

In the current study, an attempt was made to extract starch from of Jack fruit seed powder and to prove its super disintegrant nature by formulating fast dissolving tablets (FDTs).

MATERIALS AND METHODS

Materials

Telmisartan was a gift sample from Mylan Laboratories Ltd. (Hyderabad, India). Sodium hydroxide, magnesium stearate and talc were procured from S. D Fine Chem. Ltd. (Mumbai, India). Isopropyl alcohol was obtained from High Pure Fine Chem. (Chennai, India); CCS was a gift from M/s Natco Pharma Ltd. (Hyderabad, India) and Jack fruit seed were procured from the local market (Guntur, Andhra Pradesh, India). Extraction of starch from jack fruit seeds

Jack fruit seed starch was isolated using aqueous and alkali extraction techniques [7]. 5g of Jack fruit seed flour was added into 1.00 ml distilled water, 0.1%, 0.25% and 0.5% sodium hydroxide solutions separately and soaked (6 h and 8 h) at room temperature with constant stirring. The slurry was filtered through 212 mesh stainless sieve and sediment was washed with distilled water for three times. The filtrates were combined and precipitated overnight at 4°C. The supernatant was discarded and the crude starch was cleaned with distilled water. This step was repeated three times and the starch cake was dried at 40°C for 24h in oven dryer. The starch was ground with a mortar and pestle. The starches were packed in a plastic bag and kept at room temperature until further use.
Phytochemical tests for jack fruit seed powder and extracted starches

The raw jack fruit seed powder and starches extracted were subjected to various phytochemical tests for identification of carbohydrates, proteins, alkaloids, glycosides, steroids, flavonoids and saponins [8].

Evaluation of physicochemical properties of jack fruit seed powder and extracted starches

Various physicochemical properties like gelatinization temperature, pH, viscosity, swelling index and water absorption index were evaluated using suitable methods [9].

The total microbial load of isolated starch

The total microbial load is an important parameter which decides the suitability of a substance for use as an excipient in the pharmaceutical dosage form. The starch powders were subjected to dry heat sterilization at 180 °C for 30 min. Then the starches were inoculated on medium and were incubated for 24h. Then the colonies were counted using a microbial colony counter.

Formulation of telmisartan fast dissolving tablets

Telmisartan fast dissolving tablets were prepared by wet granulation technique. Isopropyl alcohol was used as a granulating fluid. The weight of all fast dissolving tablet formulations was maintained uniformly using microcrystalline cellulose as diluent. Fast dissolving tablet formulations were formulated using various concentrations of optimized extracted jack fruit seed starch and croscarmellose sodium. The drug concentration was maintained constant while jack fruit seed starch and croscarmellose sodium concentrations were varied. The compositions of various tablet formulations were given in table 4. The raw materials were individually weighed and then converted into damp mass using isopropyl alcohol. The damp mass was passed through sieve no. 20 to obtain granules and then dried. The prepared granules were passed through sieve no. 40. The granules were taken into the plastic bag and lubricated with talc, magnesium stearate and half of the starch. Then they were compressed as tablets using CLIT 10 station mini-press. To minimize the processing variables, all batches of tablets were compressed under identical conditions.

Evaluation of pre-compression parameters

The prepared granules were evaluated for pre-compression parameters such as the angle of repose, Carr's index and Hausner's ratio [10].

Evaluation of post-compression parameters

The compressed tablets were further evaluated for post-compression parameters such as weight uniformity, hardness, friability, wetting time, dispersion test and drug content [11].

Drug content uniformity

Fast dissolving tablets of Telmisartan from a batch were taken at random and was crushed to a fine powder. The powdered material was transferred into a 100 ml volumetric flask and few ml of methanol was added to it. It was shaken occasionally for about 30 min and the volume was made up to 100 ml by adding methanol. The resulting solution was set aside for few minutes and the supernatant solution was collected, filtered by using Whatman filter paper. Then the filtrate was subsequently diluted with phosphate buffer pH 7.5 with 0.5% SLS as dissolution medium and the absorbance was measured at 295 nm.

In vitro dissolution studies of telmisartan fast dissolving tablets

Dissolution studies for each tablet formulation were performed in a calibrated 8 station dissolution test apparatus (LABINDIA DS8000) equipped with paddles (USP apparatus II method) employing 900 ml of phosphate buffer pH 7.5 with 0.5% SLS as dissolution medium. The paddles were operated at 50 rpm and the temperature was maintained at 37±1 °C throughout the experiment. The samples were withdrawn at 5, 10, 15, 20, 30, 45 and 60 min and replaced with an equal volume of same dissolution medium to maintain the constant volume throughout the experiment. The amount of the drug dissolved in the withdrawn samples was estimated by Lab India double beam U. V spectrophotometer (UV 3000+) at 295 nm. The dissolution studies on each formulation were conducted in triplicate.

Statistical analysis

The results obtained were statistically evaluated. As the procedures performed and the results obtained were in triplicates, the mean along with their standard deviations (SD) was calculated for hardness, weight uniformity, drug content and standard error of means (SEM) for drug dissolution profiles.

Characterization studies

Based on the dissolution studies, the optimized formulations were selected, and FTIR and DSC studies were performed to observe the drug-polymer interactions. XRD studies were performed to detect the nature of formulations. SEM analysis was performed on Jack fruit seed powder, JFS2, Telmisartan pure drug, a blend of Telmisartan with JFS2 and a blend of Telmisartan with CCS to know surface characteristics.

Accelerated stability studies

Accelerated stability studies were carried out on optimized formulations (F5 and F11) as per International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. After the stability studies, the formulations were evaluated for physical parameters, drug content, and drug release studies.

RESULTS AND DISCUSSION

Extraction of starch from jack fruit seeds

Starches extracted from jack fruit seed powder were crisp, slightly granular, off white, free-flowing and stable in nature.

Phytochemical screening of jack fruit seed flour and starch extracts

The raw jack fruit seed powder and starches extracted from it were screened for the presence of various phytochemical components. All starches extracted showed the presence of only carbohydrates and polysaccharides. The results were indicated in table 1.

Physicochemical parameters of jack fruit seed flour and starch extracts

Physicochemical parameters were evaluated for all the starches. The results were indicated in table 2. The formulation JFS2 showed high swelling index and water absorption index, which made it suitable for preparation of fast dissolving tablets.

| Test               | JFS1 | JFS2 | JFS3 | JFS4 |
|--------------------|------|------|------|------|
| Carbohydrates      | +    | +    | +    | +    |
| Polysaccharides    | +    | +    | -    | -    |
| Proteins           | +    | -    | -    | -    |
| Alkaloids          | +    | -    | -    | -    |
| Glycosides         | +    | -    | -    | -    |
| Steroids           | +    | -    | -    | -    |
| Flavonoids         | -    | -    | -    | -    |
| Saponins           | -    | -    | -    | -    |

**+ indicates present; - indicates absent**
The pre-compression parameter values obtained for various prepared granules were given in Table 5. The angle of repose, Carr's index and Hausner's ratio values obtained for various prepared granules were within the range specified. Thus all the prepared granules were found to be stable and suitable for compression as fast-dissolving tablets.

### Table 5: Pre-compression parameters of prepared granules of various fast dissolving tablet formulations

| Formulation | Angle of repose (°) | Carr’s index (%) | Hausner’s ratio |
|-------------|---------------------|------------------|-----------------|
| F1          | 32                  | 19               | 1.22            |
| F2          | 25                  | 14               | 1.19            |
| F3          | 23                  | 13               | 1.20            |
| F4          | 21                  | 12               | 1.16            |
| F5          | 25                  | 13               | 1.18            |
| F6          | 33                  | 18               | 1.22            |
| F7          | 31                  | 18               | 1.21            |
| F8          | 26                  | 16               | 1.20            |
| F9          | 23                  | 14               | 1.19            |
| F10         | 21                  | 13               | 1.15            |
| F11         | 24                  | 14               | 1.17            |

### Table 6: Post compression parameters of various telmisartan fast dissolving tablet formulations

| Formulation | Weight uniformity (mg/tablet) (mean±SD) | Hardness (kg/cm²) (mean±SD) | Friability (% loss) | Wetting time (sec) | Dispersion time (sec) | Drug content (mg/tablet) (mean±SD) |
|-------------|----------------------------------------|----------------------------|---------------------|-------------------|----------------------|-----------------------------------|
| F1          | 251±0.24                               | 3.1±0.41                  | 0.3                 | 140               | Passed               | 19.54±0.54                        |
| F2          | 250±0.47                               | 3.5±0.24                  | 0.2                 | 120               | Passed               | 18.91±1.20                        |
| F3          | 250±0.18                               | 3.0±0.57                  | 0.2                 | 90                | Passed               | 18.55±0.61                        |
| F4          | 249±0.72                               | 3.2±0.44                  | 0.2                 | 70                | Passed               | 18.78±0.81                        |
| F5          | 249±0.81                               | 3.5±0.46                  | 0.4                 | 60                | Passed               | 19.52±0.22                        |
| F6          | 250±0.66                               | 3.2±0.98                  | 0.2                 | 220               | Passed               | 19.46±0.19                        |
| F7          | 251±0.77                               | 3.0±0.83                  | 0.3                 | 146               | Passed               | 18.34±0.40                        |
| F8          | 250±1.02                               | 3.2±0.70                  | 0.4                 | 130               | Passed               | 18.51±1.01                        |
| F9          | 249±0.54                               | 3.2±0.55                  | 0.3                 | 100               | Passed               | 17.10±0.74                        |
| F10         | 250±0.98                               | 3.5±0.87                  | 0.2                 | 85                | Passed               | 18.27±0.62                        |
| F11         | 249±0.20                               | 3.2±0.37                  | 0.3                 | 65                | Passed               | 19.32±0.87                        |

n=3; SD—standard deviation
Evaluation of post-compression characteristics of fast dissolving tablets

The compressed tablets were further evaluated for post-compression parameters and the results were given in Table 6. Weight uniformity, hardness and friability loss of all tablet formulations were within the specified limits. Of all, the wetting time for F5 and F11 formulations were less, which is a preliminary indication that these formulations were optimum. Thus all the batches of tablet formulations were found to be stable and suitable for further studies.

In vitro dissolution studies of Telmisartan fast dissolving tablets

Dissolution studies were carried on all the fast dissolving tablet formulations by using U. S. P paddle method (apparatus II) with phosphate buffer pH 6.8 as dissolution medium by maintaining the bath temperature at 37±1 °C and while the paddles water-soluble at 50 rpm. The dissolution profiles of all the fast dissolving tablets were shown in fig. 1-2. It was observed that as the type of starch as a super disintegrant and the proportion of super disintegrant have greatly influenced the dissolution parameters of various formulations. The super disintegrant JFS2 has exhibited comparative dissolution profile with that of standard super disintegrant CCS. Formulation F5 containing 15% w/w JFS2 as super disintegrant exhibited similar dissolution profile with that of formulation F11 prepared by 15% w/w CCS. Several studies have been conducted earlier, indicating the effect of super disintegrants over solubility enhancement [13]. They suggest the usage of a mixture of super disintegrants rather than single [14]. Recent studies suggest the application of natural starches as super disintegrants [15-17]. They also prove the equal efficacy of natural starches and already established super disintegrants.

Characterization of telmisartan fast dissolving tablets

Fourier-transform infrared (FT-IR) spectroscopic analysis

The FTIR spectral investigations were carried out on pure drug of Telmisartan, JFS2, CCS, Fast dissolving tablets of Telmisartan F5 and F11. Telmisartan pure drug showed a broad peak at 3143.31 cm⁻¹ and sharp peaks at 2868.59 cm⁻¹, 1100.64 cm⁻¹ and 862.64 cm⁻¹ indicating the presence of NH/OH stretching, CH stretching, C-N/C-O-C cyclic ether stretching and aromatic CH stretching. Starch extracted from jack fruit, JFS2 showed peaks at 1391.18 cm⁻¹ and 860.73 cm⁻¹ indicating the presence of C-O-C stretching and Ar-H bending. Whereas CCS exhibited sharp peaks at 3235.60 cm⁻¹, 2136.42 cm⁻¹, 1606.39 cm⁻¹, 900.17 cm⁻¹ and 736.24 cm⁻¹ indicating the presence of ≡C-H stretching, ≡C≡C-stretching, C=C stretching and CH bonds of aromatic rings. Formulation F5, FDTs made with Telmisartan and JFS2 combination exhibited strong peaks at 3143.11 cm⁻¹, 1380.21 cm⁻¹, 1092.39 cm⁻¹, 860.45 cm⁻¹ indicating the presence of ≡C-H stretching, C≡C-stretching, ≡C-O-stretching and CH bonds of aromatic rings. Formulation F11, FDTs made with Telmisartan and CCS combination exhibited strong peaks at 3137.06 cm⁻¹, 1638.13 cm⁻¹, 1059.33 cm⁻¹ and 864.94 cm⁻¹ indicating the presence of ≡C-H stretching, C≡C-stretching, ≡C-O-stretching and CH bonds of aromatic rings. The detailed spectral elucidations were shown in fig. 3.
DSC thermograms

The DSC thermographic studies were carried out on pure drug of Telmisartan, JFS2, CCS. Fast dissolving tablets of Telmisartan F5 and F11. These studies exhibited an endothermic peak at 278.96 °C for Telmisartan pure drug, broad endothermic peaks for jack fruit seed starch at 68.39 °C and 312.00 °C and a sharp exothermic peak at 319.1 °C for CCS. A broad endothermic peak at 268.43 °C and a sharp endothermic peak at 59.48 °C were observed for F5 formulation, an FDT made with Telmisartan and JFS2, indicating that there is a slight shift in temperature for drug and JFS2. A sharp endothermic peak at 274.22 °C and a broad exothermic peak at 314.7 °C were observed for formulation F11, an FDT made with Telmisartan and CCS was observed indicating that there is a slight shift in temperature for drug and CCS. The detailed thermographs were shown in fig. 4.

SEM images

SEM images were taken for Jack fruit seed powder, Telmisartan pure drug, JFS2, CCS, a blend of Telmisartan with JFS2 and a blend of Telmisartan with CCS. It was observed that the starch grains in Jack fruit seed powder were covered with some mucilage or resinous mass which were clearly represented in the image. The JFS2 starch exhibited a free-flowing spherical low dense form of starch grains without any mucilage/resinous coverage. Telmisartan pure drug exhibited crystalline form. CCS exhibited blunt tubular-shaped crystals. The SEM image of Telmisartan with JFS2 clearly exhibited uniform dispersion of drug with spherical globular starch grains. The SEM image of Telmisartan with CCS showed uniform dispersion of drug with blunt tubular crystals of CCS. The complete adhesion of natural agent with drug enhances solubility property of the poorly water-soluble drug. This was also supported by the earlier studies [18]. The detailed SEM images were shown in fig. 5.

Powder X-Ray diffractograms

XRD studies were carried out for pure drug of Telmisartan, JFS2, CCS, fast dissolving tablets of Telmisartan F5 and F11. The X-ray diffractogram of Telmisartan showed sharp and intense peaks at diffraction angles (2θ) of 19.957 ° and 21.240 ° indicating a typical crystalline pattern. Whereas JFS2 showed intense peaks at diffraction angles (2θ) of 18.548 °, 24.142 ° and 28.327 ° indicating crystalline nature. CCS showed sharp and intense peaks at diffraction angles (2θ) of 21.770 °, 22.741 °, 25.292 ° and 30.210 ° indicating crystalline nature. Formulation, F5 which is a FDT of Telmisartan and JFS2 showed sharp and intense peaks at diffraction angles (2θ) of 19.542 ° and 24.530 ° indicating the disappearance of some of the crystalline peaks of drug and JFS2 which suggest the formation of a new solid phase. Formulation, F11 which is a FDT of Telmisartan and CCS showed sharp and intense peaks at diffraction angles (2θ) of 21.758 °, 22.104 ° and 25.017 ° indicating disappearance of most of the crystalline peaks of drug and CCS which suggest the formation of a new solid phase with lower degree of crystallinity due to complexation. The detailed diffractograms were shown in fig. 6.
Fig. 4: DSC Thermograms: (A) Telmisartan (B) JFS2 (C) CCS (D) F5 (E) F11; JFS2–Jack fruit seed starch extracted by 0.1% sodium hydroxide; CCS–Croscarmellose sodium; F5–FDT of Telmisartan with JFS2; F11–FDT of Telmisartan with CCS

Fig. 5: SEM Images: (A) Jack fruit raw seed powder (B) JFS2 (C) Telmisartan, (D) CCS (E) A blend of Telmisartan and JFS2 (F) A blend of Telmisartan and CCS; JFS2–Jack fruit seed starch extracted by 0.1% sodium hydroxide; CCS–Croscarmellose sodium
Accelerated stability studies of telmisartan fast dissolving tablets

The FDTs F5 and F11 containing Telmisartan, which showed good in vitro performance were subjected to accelerated stability studies. These studies were carried out by investigating the effect of temperature on the physical properties of the tablets and on drug release from the FDTs. The results were indicated in Table 9.

The results thus indicated that there were no visible and physical changes observed in the FDTs after storage. Weight uniformity, hardness, friability, wetting time, dispersion test, and drug content were found to be uniform before and after storage at different conditions. It was also observed that there was no significant change in drug release from the FDTs. Thus, the drug release characteristics of FDTs designed were found to be quite stable.

**Table 9: Post compression parameters of formulations F5 and F11 under accelerated stability conditions**

| Formulation | Storage condition | Hardness (kg/cm²) (mean±SD) | Friability (% loss) | Dispersion test | Wetting time (sec) | Drug content (mg/tablet) (mean±SD) |
|-------------|-------------------|-----------------------------|--------------------|----------------|-------------------|-----------------------------------|
| F5          | Before storage    | 3.5±0.46                    | 0.4                | Passed         | 60                | 19.52±0.22                       |
|             | 25±2 °C, 60±5% RH | 3.4±0.98                    | 0.5                | Passed         | 61                | 19.25±0.74                       |
|             | 40±2 °C, 75±5% RH | 3.5±0.11                    | 0.4                | Passed         | 63                | 19.32±0.19                       |
| F11         | Before storage    | 3.2±0.37                    | 0.3                | Passed         | 65                | 19.32±0.87                       |
|             | 25±2 °C, 60±5% RH | 3.2±0.18                    | 0.3                | Passed         | 65                | 19.21±0.64                       |
|             | 40±2 °C, 75±5% RH | 3.2±0.04                    | 0.3                | Passed         | 67                | 19.25±0.23                       |

n=3; SD-standard deviation
CONCLUSION
The starch JFS2, extracted by 0.1% sodium hydroxide, is found to be best and is used as a super disintegrant for preparation of fast dissolving tablets. Telmisartan FDTs were prepared using various concentrations of JFS2 and CCS and were subjected to in vitro dissolution studies which showed best drug release. Based on the above studies, the super disintegrant nature of jackfruit seed starch was proved.

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AUTHORS CONTRIBUTIONS
Dr. Vidyadhara suryadevara the guarantor of this study has designed and supervised the experimental process. Mr. Sundeep mupparaju and Mr. Sandeep doppalapudi have carried out the experiment, analyzed the results and contributed in preparation and revision of manuscript. Dr. Sasidhar reddyvallam L C and Dr. Siva prasad sundara have reviewed the manuscript.

CONFLICTS OF INTERESTS
The authors declare no conflicts of interest

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