Original Article

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Cramming on potato starch as a novel superdisintegrant for depiction and characterization of candesartan cilexetil fast dissolving tablet

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ABSTRACT

Background: In the current investigation, a strive became finished to synthesis a novel polymer, starch tartrate by treating potato starch with tartaric acid and utilize it as superdisintegrant for designing candesartan cilexetil (CC) fast-dissolving tablets. Starch tartrate was synthesized from potato starch and evaluated for phytochemical tests, physicochemical properties, and acute toxicity studies. CC tablets have been prepared by usage of a direct compression approach. **Results:** Acute toxicity studies on novel polymer indicated that there are no physiological changes in the rat behavior and were healthy. Formulated CC tablets were gone through pre-compression parameters, post-compression parameters, and stability studies. All the parameters were observed to be within the pharmacopeia detailed limits. It was found that the formulation of starch tartrate dissolute the drug at a faster rate when compared to other formulations ($P < 0.05$). Optimized formulation was evaluated for FTIR and DSC analysis revealed that there had been no most important incompatibilities between the active molecule and excipients. Stability research on the optimized formula confirmed the stability of the formulation. **Conclusion:** It was concluded that the novel polymer, starch tartrate synthesized from potato starch was endow to be appropriate for fast dissolving tablet preparation. The optimized formulation obtained was with decent chemical and physical properties having accelerated disintegration and onset of action.

Keywords: Candesartan cilexetil, fast dissolving tablets, potato starch, starch tartrate, superdisintegrants

BACKGROUND

Fast dissolving tablets (FDTs) have been prepared as an alternative to traditional tablets, principally considering children and old age patients suffer who undergo swallowing stable dosage bureaucracy.[1] FDTs dominate accurate dosing, fast onset of action, and speedy disintegration and dissolution within the buccal cavity avoiding water assistance. Further FDTs have the aid of escaping the pre-systemic effect that occurs all through stomach absorption. FDTs can boost the safety and bioavailability profiles of APIs that altered inside the liver to harmful by-products. The FDTS could be suitable for neuroleptics, analgesics, antiallergics, cardiovascular agents, and erectile dysfunction.[2]

Several approaches such as molding, spray drying, lyophilization, sublimation, vacuum drying, and direct compression were used for the preparation of FDTs.[3,4] Among all the techniques direct compression is the most convenient process for continuous tablet manufacturing. Many benefits such as demand flexibility scale up or down, batch size adaptivity, increased manufacturing ability, and limited operational footprint made direct compression superior over other approaches. Many FDTs contain fast disintegrating agents which include starch by-products, cellulose products, and fabricated agents were studied for their impact on tablet disintegration.[5-7] Many FDTs contain crospovidone, sodium starch glycolate, and croscarmellose sodium as superdisintegrants to enhance fast disintegration.[8] Most of the FDTs are eminently friable by virtue of its structural porosity and to bypass these, co-processed excipients can be used in the formulation and will be able to produce mechanically hard FDTs. The particle-particle repulsive force

and disintegration mechanisms of tablets containing starch coprocessed superdisintegrant were explored.[9]

The previous reports illustrate the possibility of exploring superdisintegrants out of natural sources some of these are *Lepidium* sativum mucilage,[10] Ocimum mucilage,[11,12] Fenugreek seed mucilage,[13] Plantago ovate seed mucilage,[14] Jackfruit seeds starch,[15] and *Hibiscus rosa-sinensis* Linn.[16,17] Mucilage and mango peel pectin; they are eco-friendly, non-toxic, widely available, and economical. However, extraction and purification of products from natural sources may be a time-consuming process and may produce stability problems. To overcome, these difficulties utilizing semi-synthetic (novel) products seem to be more beneficial, which may be less toxic than synthetic one and more stable than the natural products.

Candesartan cilexetil (CC) is a selective AT1 subtype antagonist II receptor antagonist. It is an ester pro-drug hydrolyzed to candesartan during gastrointestinal absorption.[18] Candesartan acts by blocking angiotensin II aldosterone secreting and vasoconstrictor effects by blocking angiotensin II to AT1 binding in tissue such as adrenal gland and vascular smooth muscles.[19] It belongs to BCS Class II drugs possessing low solubility, and with the elimination half-life of 8–12 h. After oral administration, CC showed low bioavailability in humans acknowledging its low solubility and first-pass metabolism by cytochrome P450 3A4.[20-25] Thus, there is a need for a promising dosage form that delivers CC promptly to the patient, resulting in better therapy. Relay on the biopharmaceutical and pharmacokinetic properties specified above, CC was chosen as a drug candidate for designing FDTs.

In the current study, an effort was done to synthesis novel polymer from potato starch and used as superdisintegrant to examine the feasibility of designing FDTs. CCFDT were formulated by taking crospovidone, croscarmellose sodium, and starch tartrate as superdisintegrant by direct compression method.

METHODS

Materials

CC from college store, crospovidone, and croscarmellose sodium from Yarrow chemic products Pvt. Ltd, India. Potato starch, sodium lauryl sulfate, and saccharine sodium from Loba chemic Pvt. Ltd, Mumbai. Microcrystalline cellulose from Merck Pvt. Ltd, Mumbai. Magnesium stearate and mannitol from S.D. Fine Chem Pvt, Ltd, Mumbai and Talc from Kemphasol laboratory, Bombay.

Preparation of Starch Tartrate (Novel Polymer)

Synthesis of starch tartrate from potato starch

Tartaric acid weighing 20 g was dissolved in 50 ml of water and the pH was adjusted to 3.85 with 10 M sodium hydroxide. To this 20 g of potato starch was added and conditioned for 20 h at room temperature. It was kept at 60°C until drying. The dried product obtained was ground and repeatedly washed with distilled water. It was again dried at 60°C and passed through sieve no 85.

Phytochemical tests for starch tartrate

Starch tartrate was subjected to phytochemical tests for the identification of carbohydrates, proteins, alkaloids, glycosides, steroids, carbonyl groups, and ester groups by various tests such as Molisch's test, Mayer's test, and biuret test.[26]

Evaluation of physicochemical properties of synthesized starch tartrate

Solubility

The solubility of starch tartrate was tested in water, aqueous buffers of pH 1.2, 6.8, 7.4, and 7.5, and organic solvents such as methyl alcohol, chloroform, acetone, and ethers.

Gelling property

The gelling property of novel polymer was assessed by warming 10% w/v dispersion in water for 15 min at 100°C.

Viscosity

The viscosity of 1% w/v dispersion in water of synthesized starch tartrate was estimated using Ostwald viscometer (Lab Indian Istruments private limited, Haryana India).

Determination of pH

The pH of the synthesized starch tartrate was estimated using a digital pH meter (Lab Indian Instruments private limited, Haryana India).

Melting point

The melting point of the synthesized starch tartrate was determined using the melting point apparatus (Shital Scientific Industries).

Swelling index

Prepared starch tartrate (200 mg) was taken in two different graduated test tubes. 10 ml of water and light liquid paraffin was added to the starch tartrate and blended. The dispersion in the tubes was permitted to settle for 12 h. The sedimented volumes were recorded and the swelling index was calculated.[27]

$$\text{Swelling index} = \frac{\text{volume of sediment in water-}}{\text{volume of sediment in light liquid paraffin}} \quad (1)$$

Flow properties

Prepared starch tartrate was evaluated for flow property parameters such as angle of repose, Hauser's ratio, and Carr's index.

Characterization of novel polymer

FTIR spectra of potato starch and starch tartrate were obtained using FTIR of Agilent carry 360: series. 2–4 mg of sample powder was scanned over 4000–400 cm^{-1} and obtained data were analyzed.

Acute toxicological studies of novel polymer in rats

Thirty healthy adult male Wistar rats (260–320 g) were selected randomly for the experiment. These rats were obtained from Mahaveer Enterprises (Hyderabad, India). These animals were placed under ideal laboratory conditions as per the guidelines of OECD for 1 week before the experimentation.

These rats were randomly divided into six groups, each group containing five rats were used in the study. All the animals were administered with different starch doses (100 mg/kg, 500 mg/kg, 1000 mg/kg, 2000 mg/kg, and 200 mg/kg (std) body weight) to different groups, these were fed once orally. After the completion of the experimentation protocol, animals were placed under a laboratory environment for the next 10 days with normal feed. All the animals were observed continuously for changes in any behavior or physical activities after the dose administration. After the completion of the experimental protocol, the rats were placed under ideal laboratory conditions. The same animals were utilized for other protocols after the washout period.

Table 1: Phytochemical test for synthesized starch tartrate

Phytochemical constituents	Chemical tests	Novel polymer
Test for carbohydrates	Molisch test	Positive
	Benedict's test	Positive
	Barfoed's test	Positive
Tests for polysaccharides	Iodine test	Positive
Tests for proteins	Biuret test	Positive
Tests for alkaloids	Mayer's test	Positive
Test for glycosides	Keller-Kiliani test	Positive
Test for steroids	Salkowiesk test	Positive
	Liebermann-Burchard test	Positive
Test for carbonyl groups	Tollen's test	Positive
Test for esters	Phenolphthalein's test	Positive
Test for flavonoids	Ferric chloride test	Negative
	Lead acetate test	Negative
Test for saponins	Foam test	Negative

Starch tartrate was prepared by treating potato starch with tartaric acid

Table 2: Physicochemical properties evaluation of synthesized starch tartrate

Parameters	Novel polymer
Solubility	In soluble in aqueous and organic solvents
Gelling property	No gelling even at a temp of 100°C
Viscosity	1.22cps
pH	3.85
Melting point	Charred at 270°C
Swelling index	66.6
Bulk density	0.625 g/cc
Tapped density	0.714 g/cc
Angle of repose	$23^{0}.8^{1}$
Carr's index	12.46%
Hausner's ratio	1.14

Starch tartrate was prepared by treating potato starch with tartaric acid

Table 3: Acute toxicological studies of starch tartrate in Wistar rats

Group	Dose (mg/kg body weight)	Mortality (X/N)	Symptoms
Control	-	0/5	Normal
I	100	0/5	Normal
II	500	0/5	Normal
III	1000	0/5	Normal
IV	2000	0/5	corner sitting
V	200	0/5	Normal

Preparation of CC FDTs

CC FDTs had been formulated through the direct compression method.[28] Drug and the excipients were sieved via sieve no. 44 having the pore size of 437 microns for ensuring even particle size. API along with the excipients, except magnesium stearate are mixed thoroughly for 15 min using a polybag. The ensuing mixture was blended with magnesium stearate. The blended powder was compressed directly by tablet compression machine (Cad Mach Machinery Co. Pvt. Ltd., India) utilizing 8 mm circular tooling.

Micromeritic evaluation of granules

Before compression, the granule blends of the formulations were oppressed for bulk density, tapped density, Hausner ratio, Carr's index, and angle of repose. USP Method I was utilized for determination of bulk density, whereas USP Method II with tapped density tester (Aymes, Turkey) was utilized to determine tapped density. Following equations were utilized for calculation of Hausner ratio, Carr's index, and angle of repose.

$$Hausner\ ratio = Tapped\ density/bulk\ density \quad (2)$$

$$Carr's\ index\ \% = (Tapped\ density - bulk\ density)*100/tapped\ density \quad (3)$$

$$Tan\ \theta = 2h/D \quad (4)$$

Scanning electron microscopy

Surface image of starch tartrate, pure drug and blend of drug, and starch tartrate were obtained at different magnifications using an electron microscope (XL30ESEM with EXAX). SEM analysis was conducted by preparing and placing samples on aluminum pin stubs under vacuum.

Differential scanning calorimetry

Differential scanning calorimetry measurements of pure drug, physical mixture of drug and starch tartrate, and optimized formulation were obtained using the Mettler Toledo DSC 821e instrument. 3–6 mg of sample was filled into a sample pan and sealed. The samples were scanned between 30°C and 350°C at a heating rate of 10°C/min.

Characterization of CC FDTs

Weight variation

Twenty tablets were randomly chosen from all the formulation and weighed separately. For determining the weight variation, each and individual weights were compared with the average weight.

Hardness measurement

The crushing endurance of FDTs, which is the strength needed to break a tablet by radial direction compression, was measured using tablet hardness tester (Monsanto tablet tester)

Table 4: Composition of candesartan cilexetil fast dissolving tablets with crospovidone, croscarmellose, sodium, and starch tartrate

Ingredients (mg/tablet)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Candesartan cilexetil	4	4	4	4	4	4	4	4	4
Crospovidone	6	8	10	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	6	8	10	-	-	-
Starch tartrate	-	-	-	-	-	-	6	8	10
Micro crystalline cellulose	60	60	60	60	60	60	60	60	60
Saccharine sodium	3	3	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2	2	2
Sodium lauryl sulfate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Mannitol	121	119	117	121	119	117	121	119	117

Starch tartrate was prepared by treating potato starch with tartaric acid

Friability measurement

Priorly measured ten tablets were placed in the friabilitor (Roche friabilitor). The friabilitor was rotated at 25 rpm, and the percentage friability was calculated.

Wetting time

The wetting time of formulation connected to the contact angle of the dosage form. The wetting time of CCFDT is another main parameter needed to be evaluated to give knowledge on the disintegration mechanism of the formulation. Lower wetting time indicates faster disintegration of the formulation. This is determined by utilizing five circular tissue papers having a 10 cm diameter kept in the Petri dish. Add 10 ml of water-soluble dye on the tissue paper. Place the formulation prudently on the tissue paper, record the time necessary for the water-soluble due to extend the upper surface of the formulation.

Water absorption ratio

Take 6 ml of purified water in a Petri dish with 5.5 cm of internal diameter; add a piece of tissue paper folded twice. Complete wetting of tablet was permitted by placing on the tissue paper. The water absorption ratio of the tablet was determined by the reweighing of the wetted tablet.

$$\text{Water absorption ratio} = \frac{(\text{weight before wetting} - \text{weight after wetting})}{\text{weight before wetting}} 100 \quad (5)$$

Drug content

Prepared CC FDTs were taken at random and were powdered using mortar and pestle. Transfer the powder equivalent to 200 mg of the drug into a 100 ml volumetric flask. Dissolve the powder in 6.8 pH phosphate buffer by sonication. The volume was made up to the mark with buffer. The filtered solution (undissolved matters were removed by filtration through Whatman No.1 filter paper) was analyzed for drug content using UV-visible spectrophotometer (Thermo Scientific labs) at 262 nm.

In vitro dissolution studies

In vitro dissolution study experiments were conducted in triplicate at 37°C utilizing the USP II apparatus. 900 ml of pH 6.8 buffer with a rotational speed of paddle with 50 rpm were utilized for the study. 5 ml of the sample was drawn from the dissolution medium at specific time intervals. An equal amount of dissolution fluid was replenished in the medium for maintaining sink condition. The absorbance of the filtered and diluted samples was deliberated by utilizing UV-spectrophotometer.

FTIR Analysis

FTIR spectra of potato starch, starch tartrate, pure drug, and a different formulation were obtained using FTIR of Agilent carry 360: Series. 2–4 mg of sample powder was scanned over 4000–400 cm^{-1} and obtained data were analyzed.

Kinetics of drug release

The *in vitro,* dissolution profile of all batches was fitted to zero-order, first-order, and Higuchi model to ascertain the kinetic modeling of drug release. Correlation coefficient (R^2) values were calculated for linear curves obtained by the regression analysis.[29,30]

Zero-order Eq. $M_t = k_O t$ (6)

First-order Eq. $log\ M_0 - log\ M_t = k_1\ t/2.303$ (7)

Higuchi Eq. $Mt = k_H \sqrt{t}$ (8)

Korsmeyer–Peppas Eq. $Log\ (M_t/M_\alpha) = log\ k + n\ log\ t$ (9)

Where t indicates time, M_t indicates the amount of drug release at time t, M_0 indicates the initial amount of drug, k_O indicates zero-order rate constant, k_1 indicates first-order rate constant, and k_H indicates Higuchi constant.

Stability studies

Stability studies for optimized formulation were conducted based on the International Council for Harmonization[31] guidelines. After conducting these stability studies, the formulation was evaluated for physical properties, medicament release, and drug content estimation.

Statistical Analysis

The values are expressed in mean ± S.D. Graph Pad Instat software, Version 3.01 was used to analyze data using one-way ANOVA, followed by multiple comparison test. $P < 0.05$ was considered significant.

RESULTS

Phytochemical Composition of Starch Tartrate

Starch tartrate was prepared by reacting starch with tartaric acid at elevated temperature. An equal amount of starch and tartaric acid was reported optimum for the preparation of starch tartrate. Starch tartrate was found to be white amorphous, non-hygroscopic powder which passes through sieve no. 85 and retained on sieve no.120 was collected.

Starch tartrate was assessed for the existence of carbohydrates, proteins, polysaccharides, alkaloids, steroids, glycosides, carbonyl group, ester groups, saponins, and flavonoids. A positive outcome from the Molish test, confirmed the existence of carbohydrates in the prepared polymer. A positive outcome from the Tollens test, confirmed the existence of the carbonyl group in starch tartrate. The existence of the ester group in the polymer was confirmed by the positive result of the Phenolphthalein's test. The results are given in Table 1.

Physicochemical Properties of Starch Tartrate

The outcomes of the physicochemical properties confess that polymer prepared was insoluble in water, chloroform, methanol, and acetone. The pH of starch tartrate dispersion (1% w/v aqueous) was found as 3.85. The prepared polymer was not melted but charred at 270°C. The viscosity of 1% aqueous dispersion of starch tartrate was determined as 1.22 cps and the swelling index was confirmed to be 66.6. Gelling was not observed with an aqueous dispersion of starch tartrate when heated at 100°C for 15 min, whereas gelling was found in potato starch during the above heat treatment. The starch tartrate prepared was characterized by determining various physical properties. The bulk density and tapped density of the prepared polymer were determined to be 0.625 and 0.714, respectively. The angle of repose of 23.8, compressibility index value of 13.54, Carr's index value of 12.46, and Hausner's ratio value of 1.14 revealed the good flow properties of starch tartrate. The results are given in Table 2.

Characterization of Novel Polymer

The FTIR spectra of potato starch and starch tartrate are shown in Figure 1. The FTIR spectra of starch tartrate produce a peak at 1717.40 cm^{-1} indicate C=O carbonyl stretching in ester group, a peak at 1783.76 cm^{-1} indicates C=O stretching in ester group which were not appeared in potato starch.

The electro micrograph for starch tartrate is shown in Figure 2. The electro micrographs for starch tartrate revealed the cylindrical as well as oval-shaped morphology with smooth surface which may be possible of having free flowing nature. It comprised irregular shapes and large sizes. The electro micrographs for the starch tartrate recommend the existence of amorphous aggregates with irregular size. The conduct is as per the outcomes got utilizing heat analysis and X-ray diffraction. X-ray diffraction uncovers the physical condition of the molecule at room temperature. X-ray diffractogram for starch tartrate was shown in Figure 3. In the diffractogram for starch tartrate, there was no characteristic peak revealed the amorphous nature of the prepared polymer.

Toxicological Studies on Novel Polymer

The outcomes of the toxicological evaluations declared that there are no physiological changes in the behavior of all groups of rats up to1000 mg/kg. Corner sitting was examined in the rats at the dose of 2000 mg/kg. A higher dose did not show any death incidence of animals. The outcomes are given in Table 3.

Pre-compression Parameters of CC FDTs

Nine formulations of CC FDTs containing microcrystalline cellulose and mannitol as diluents, cross carmellose sodium, crospovidone, and starch tartrate were incorporated as disintegrants, sodium saccharin as a sweetening agent, magnesium stearate as lubricant, and talc as glidant. The compositions are given in Table 4.

The pre-compression information is presented in Table 5. The angle of repose of different formulations was found in the scope of 27°.21'±0.36–29°.81'±0.45. This demonstrates a good flow property of the blended powder. Bulk densities and tapped densities of different formulations were seen as in the scope of 0.311±0.04–0.395±0.01 (g/cc) and 0.332±0.09–0.437±0.02 (g/cc), respectively. The compressibility index of the granules was found in the scope of 6.32±0.68–11.97±0.15% demonstrate excellent compressibility. Hausner's ratio was found within the scope of 1.06 ± 0.02–1.13 ± 0.09% demonstrates that the mixture has necessary flow property and strength for compression.[32]

Characterization of FDTs

After granular compression into matrix tablets, the outcomes of post-compression parameters such as thickness, hardness, friability, weight variation, wetting time, water absorption ratio, *in vitro* disintegration, and drug content are shown in Table 6. This indicates that all the parameters were observed to be within the pharmacopeia detailed limits.

In vitro dissolution study, experiments were conducted in triplicate at 37°C utilizing the USP II apparatus. 900 ml of pH 6.8 buffer with a rotational speed of paddle with 50 rpm were utilized for the study. The pure medicament CC is shown its release up to 43.38%, whereas the marketed formulation exhibited 84.6 3% drug release in 60 min. Pure drug CC and marketed formulated formulation show the release of 26.28% and 47.72% drug release, respectively, within 10 min.

F_1, F_2, and F_3 formulations consisting crospovidone as superdisintegrant showed the drug release of 59.77 ± 2.05%, 60.4 ± 1.8%, and 79.93 ± 0.9%, respectively. These formulations showed an enhanced dissolution rate from 2.27-fold to 3.04-fold to that of pure drug CC within 10 min. F_4, F_5, and F_6 formulations consisting croscarmellose sodium as superdisintegrant showed the drug release of 47.01 ± 0.9%, 56.13 ± 1.2%, and 64.18 ± 0.7%, respectively. These formulations showed an enhanced dissolution rate from 1.78-fold to 22.4-fold to that of pure drug CC within 10 min. F_7, F_8, and F_9 formulations consisting starch tartrate as superdisintegrant showed the drug release of 70.13 ± 1.1%, 83.2 ± 0.3%, and

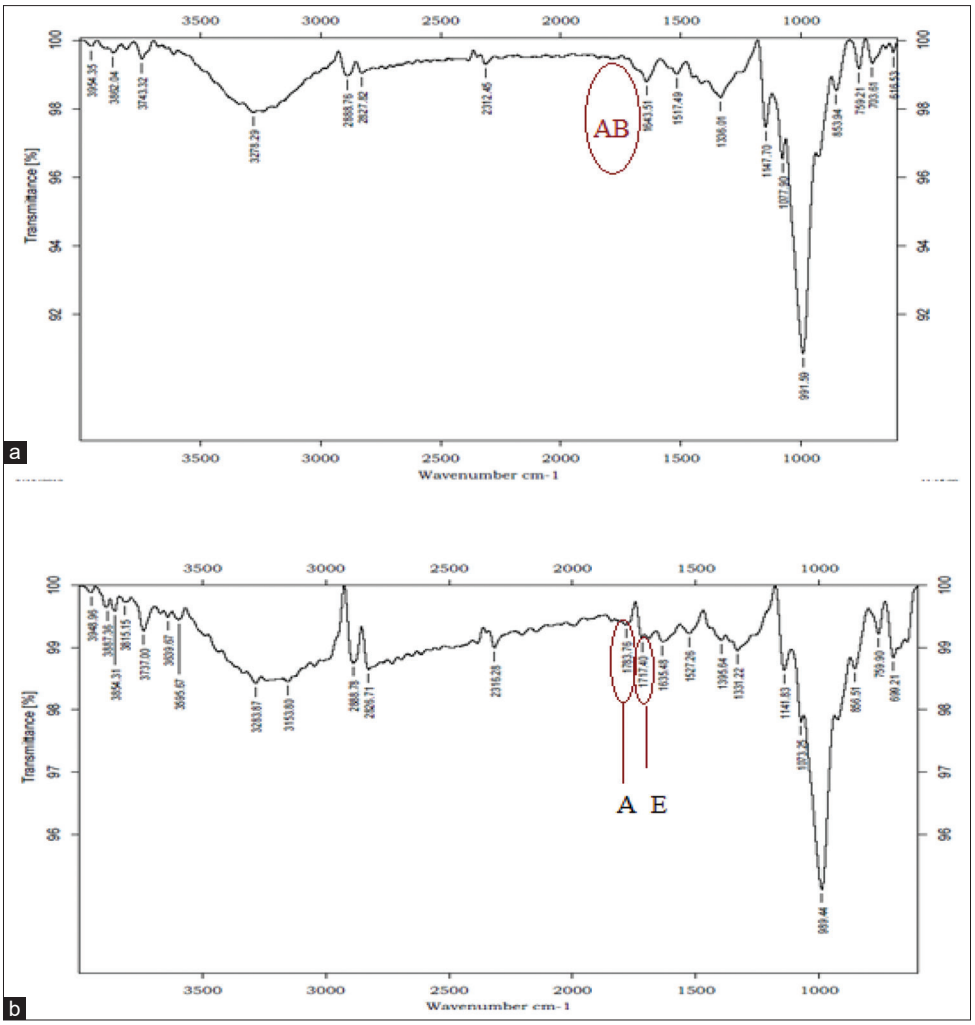

Figure 1: FTIR spectra. (a) Potato starch (AB –Absent). (b) Starch tartrate (A-acid group, E- ester group)

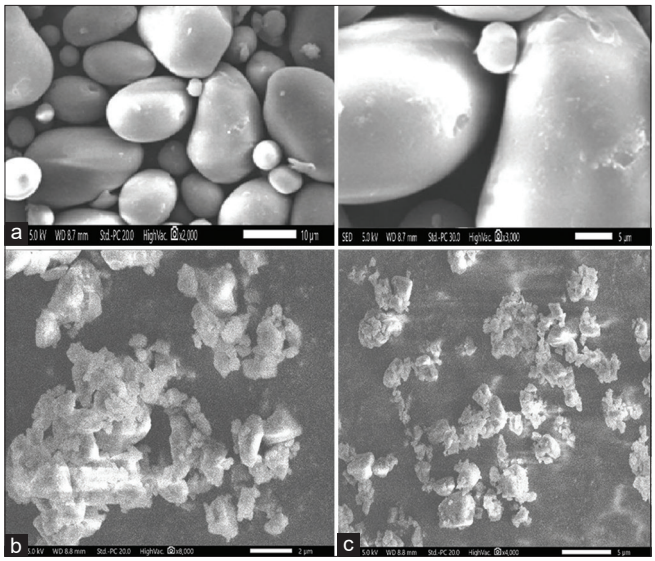

Figure 2: SEM images. (a) Starch tartrate. (b) Pure API (candesartan cilexetil [CC]). (c) Blend of CC and starch tartrate

99.2 ± 0.93%, respectively. These formulations showed an enhanced dissolution rate from 2.66-fold to 3.77-fold to that of pure drug CC within 10 min. The dissolution profiles of nine formulations are shown in Figure 4 and Table 7. The comparison of optimized formulation with marketed formulation is shown in Figure 5.

Formulation F9 consisting 5% w/w of starch tartrate as superdisintegrant released the drug CC at 99.21 ± 0.93%.

Table 5: Pre-compression parameter evaluation of prepared granules

Formulation	Angle of repose (Ø)	Carr's index (%)	Hausner's ratio
F1	29.81±0.45	6.32±0.68	1.06±0.02
F2	28.75±0.32	8.14±0.44	1.08±0.04
F3	27.32±0.16	8.14±0.25	1.08±0.01
F4	28.62±0.74	11.97±0.15	1.13±0.09
F5	28.82±0.83	9.61±0.36	1.10±0.05
F6	27.75±0.22	8.56±0.70	1.09±0.02
F7	29.75±0.64	8.13±0.69	1.08±0.04
F8	27.96±0.78	7.46±0.39	1.08±0.06
F9	27.21±0.36	6.51±0.28	1.06±0.05

Values are mean±SD of six determinations

This formulation was found to show the improved dissolution rate of 3.77-fold when compared to pure drug CC and 2.07-fold when compared to marketed formulation within 10 min. The dissolution data of CC FDTs were inspected according to zero-order, first-order equation, Peppas model, and Higuchi model to figure out the release kinetics of the active molecule, while considering kinetic modeling high R^2 signifies a fine correlation among the model and fitted values. Based on the outcomes of the data provided in Table 8, the Higuchi be in possession to best suit for dissolution data of formulations including F9. This, in turn, describes diffusion as the release mechanism and concentration acts as a main driving force in drug release.

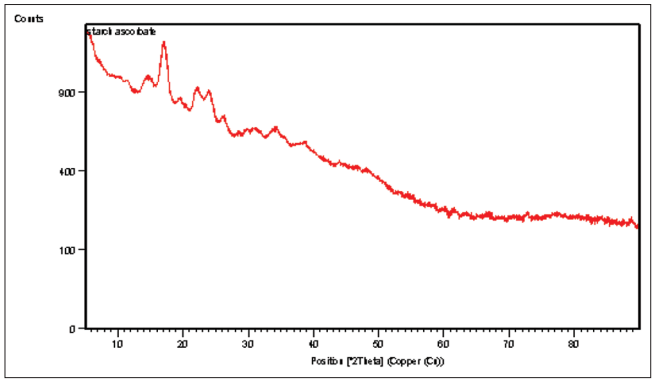

Figure 3: X-ray diffractogram of starch tartrate

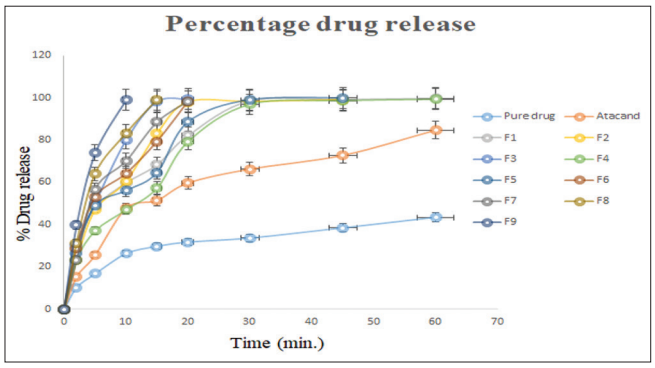

Figure 4: Dissolution profile of candesartan cilexetil fast dissolving tablet formulations containing starch tartrate in comparison with tablets containing crospovidone and croscarmellose

These dissolution studies indicated that starch tartrate obtained from potato starch was found to be promising as novel superdisintegrant for FDTs formulation for poorly soluble drug CC. The outcomes wetting time attained from starch tartrate determined that the polymer was highly hydrophilic and tends to swell moderately. The dissolution profile of F9 when correlated with marketed formulation, there is an enhancement of the dissolution parameter to that of the marketed formulation is observed.

The FTIR spectral analysis was conducted on the pure drug, potato starch, starch tartrate, blends of pure drug CC and crospovidone, pure drug and croscarmellose sodium, pure drug, and starch tartrate. These FTIR spectrums are shown in Figure 6. Pure drug CC exhibited sharp peaks at 1612.04 cm^{-1}, 1546.69 cm^{-1}, 1074.69 cm^{-1}, 2939.78 cm^{-1}, and 2860.52 cm^{-1} indicating the presence of aromatic C=C stretching, C=N stretching, CO stretching, CH stretching, and OH stretching. For pure drug and crospovidone exhibited sharp peaks at 1642.42 cm^{-1}, 1420.27 cm^{-1}, 1074.64 cm^{-1}, 2910.55 cm^{-1}, and 2851.71 cm^{-1} indicating the presence of aromatic C=C stretching, C=N stretching, CO stretching, CH stretching, and OH stretching. For pure drug CC and croscarmellose sodium exhibited sharp peaks at 1609.02 cm^{-1}, 1549.02 cm^{-1}, 1074.11 cm^{-1}, 2915.73 cm^{-1}, and 2852.12 cm^{-1} indicating the presence of aromatic C=C stretching, C=N stretching, CO stretching, CH stretching, and OH stretching. For pure drug and starch

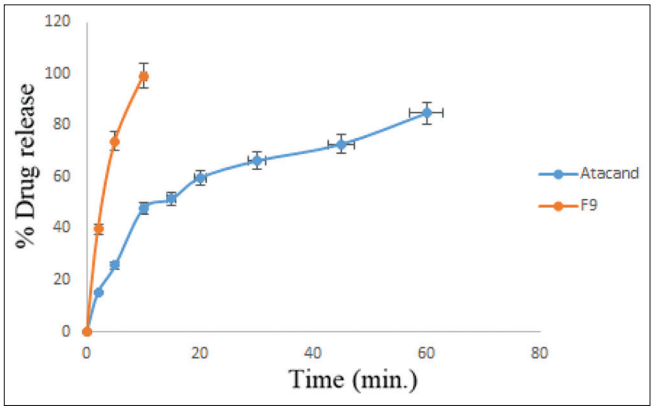

Figure 5: Dissolution profile of optimized formulations containing starch tartrate in comparison with marketed formulation

Table 6: Post-compression parameter evaluation of prepared formulations

Formulation	Weight uniformity (mg)	Hardness (kg/cm²)	Friability (%) loss	Wetting time (s)	Disintegration time (s)	Water absorption ration (%)	Content uniformity (%)
F1	196.4±0.7	3.60±0.10	0.33±0.07	48±2.08	28±1.55	56.52±1.35	98.8±0.91
F2	199.3±0.8	4.03±0.07	0.35±0.07	57±4.72	36±1.68	59.72±2.64	103.6±0.66
F3	203.9±2.2	4.95±0.08	0.34±0.04	55±3.21	26±3	60.52±0.78	99.5±1.61
F4	198.3±0.9	3.93±0.17	0.71±0.17	41±2.08	49±1	62.53±0.84	98.4±0.43
F5	197.1±1.5	3.87±0.19	0.67±0.09	40±2.01	51±1.52	61.01±0.81	102.7±0.43
F6	202.2±2.2	3.87±0.16	0.72±0.04	35±3	48±0.57	57.91±0.65	97.1±1.33
F7	201.8±1.9	4.43±0.29	0.40±0.05	34±1	24±2.51	56.42±0.63	99.2±1.24
F8	197.5±1.3	3.87±0.20	0.46±0.06	30±2	22±3.05	66.77±0.72	97.2±0.61
F9	199.4±1.9	3.50±0.30	0.55±0.02	29±1.52	19±1.73	57.98±1.05	101.8±1.11

Values are mean±SD of six determinations

Table 7: Evaluation of dissolution parameters (% drug release) for prepared Candesartan cilexetil formulations

Time (min)	Pure drug	Marketed formulation (ATACAND)	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	10.28±0.7	15.27±1.0	28.41±0.67	23.13±0.8	30.42±1.0	23.11±0.5	26.40±1.1	28.61±0.1	23.14±0.7	31.21±0.1	39.72±0.25
5	16.72±0.7	25.63±0.3	48.13±1.08	46.93±0.7	50.11±0.6	37.10±1.0	49.14±0.3	53.02±0.7	56.64±1.3	64.06±1.3	73.93±0.11
10	26.28±1.3	47.72±0.93	59.77±2.05	60.44±1.8	79.93±0.9	47.01±0.9	56.13±1.2	64.18±0.7	70.13±1.1	83.21±0.3	99.21±0.93
15	29.73±0.8	51.48±0.4	68.41±1.31	83.01±0.7	98.31±0.8	57.33±0.7	64.58±1.1	79.28±0.3	88.51±1.0	99.13±0.4	-
20	31.72±0.9	59.67±0.6	82.19±1.31	97.91±0.5	99.27±0.6	79.28±0.6	88.51±1.0	98.11±0.9	98.28±0.6	-	-
30	33.63±0.4	66.24±0.5	98.62±0.88	98.11±0.9	-	96.93±0.4	99.01±0.8	-	-	-	-
45	38.43±0.25	72.72±1.08	99.21±0.93	99.02±0.4	-	98.62±0.3	99.87±1.2	-	-	-	-
60	43.38±0.8	84.63±0.25	99.81±0.5	-	-	99.25±1.0	-	-		-	-

Values are mean±SD of six determinations

Table 8: Release kinetics of candesartan cilexetil FDTs

Formulation	Zero-order (R^2)	First-order (R^2)	Higuchi (R^2)	Peppa's (R^2)
F1	0.9572	0.8762	0.9903	0.9273
F2	0.9761	0.8732	0.9885	0.9062
F3	0.9851	0.9117	0.9968	0.9687
F4	0.9814	0.8921	0.9694	0.9576
F5	0.9331	0.8882	0.9594	0.9321
F6	0.9641	0.8243	0.9784	0.8675
F7	0.9111	0.9237	0.9676	0.8963
F8	0.9212	0.9905	0.9739	0.9624
F9	0.9481	0.9661	0.9854	0.9586

Regression analysis (release kinetics) of candesartan formulations (F1-F9)

Table 9: Stability parameters of formulation F9 stored at room temperature

Parameters	Controlled (F9)	After 1 month	After 2 months
Drug content (%)	101	98.39	98.11
Disintegration time (s)	19	20	21
Wetting time (s)	30	31	33

tartrate exhibited sharp peaks at 1612.97 cm^{-1}, 1547.96 cm^{-1}, 1074.64 cm^{-1}, 2915.44 cm^{-1}, and 2851.62 cm^{-1} indicating the presence of aromatic C=C stretching, C=N stretching, CO stretching, CH stretching, and OH stretching. The remaining peaks were not altered, which indicated the absence of drug excipient interactions.[33]

DSC studies were carried out on pure drug CC, blend of CC and starch tartrate and optimized formulation. These DSC thermograms are shown in Figure 7. Pure drug CC presented a pointed endothermic peak at 170.6°C. Blend of CC and starch tartrate presented a pointed endothermic peak at 168.48°C. Optimized formulation having 5% starch tartrate presented a pointed endothermic peak at 167.6°C. These studies confirmed the existence of similar thermographic peaks at respective temperatures, which reveals that there is no drug-excipient interaction. However, we can notice a little change in the drug peak position, which might be because of the purity reduction of blended mixture.[34]

X-ray diffraction uncovers the physical condition of a molecule at room temperature. X-ray diffractogram for starch tartrate is shown in Figure 3. In the diffractogram for starch tartrate, there was no characteristic peak, revealed the amorphous nature of the prepared polymer. The electro micrograph was taken for starch tartrate, pure drug CC, and blend of CC and starch tartrate. The electro micrographs of pure drug CC exhibited needle-like crystalline form of materials. The electro micrograph of starch tartrate revealed the cylindrical as well as oval-shaped morphology. It comprised an irregular shape with large sizes. The electro micrographs for the starch tartrate recommend the existence of amorphous aggregates with an irregular shape. The SEM image of drug and starch tartrate blend clearly indicated the homogeneous dispersion of medicament with starch tartrate. SEM images are shown in Figure 2.

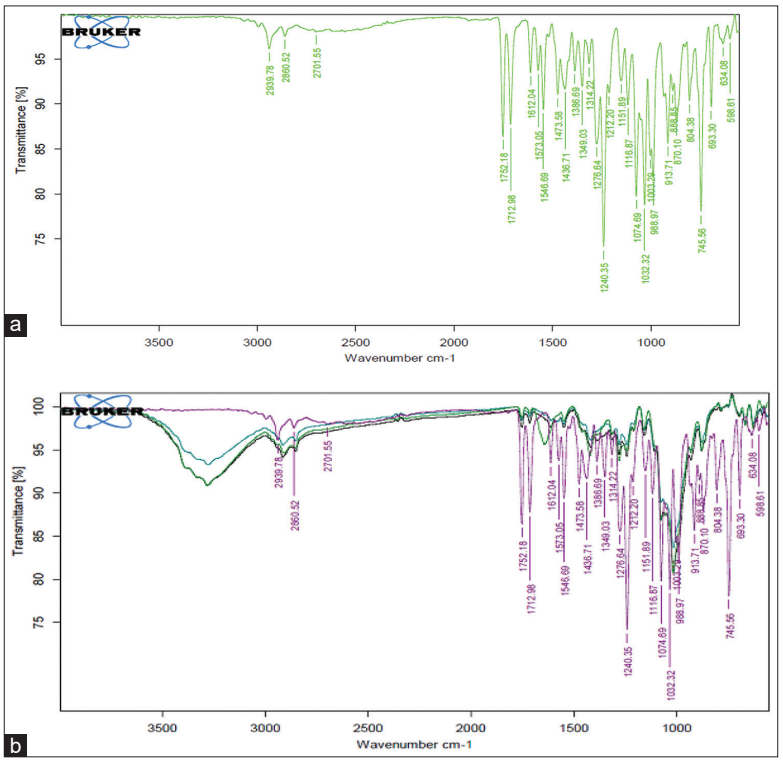

Figure 6: FTIR spectra. (a) Pure candesartan cilexetil. (b) Comparison graph of (pure API, F3, F6, and F9 – formulations 5%)

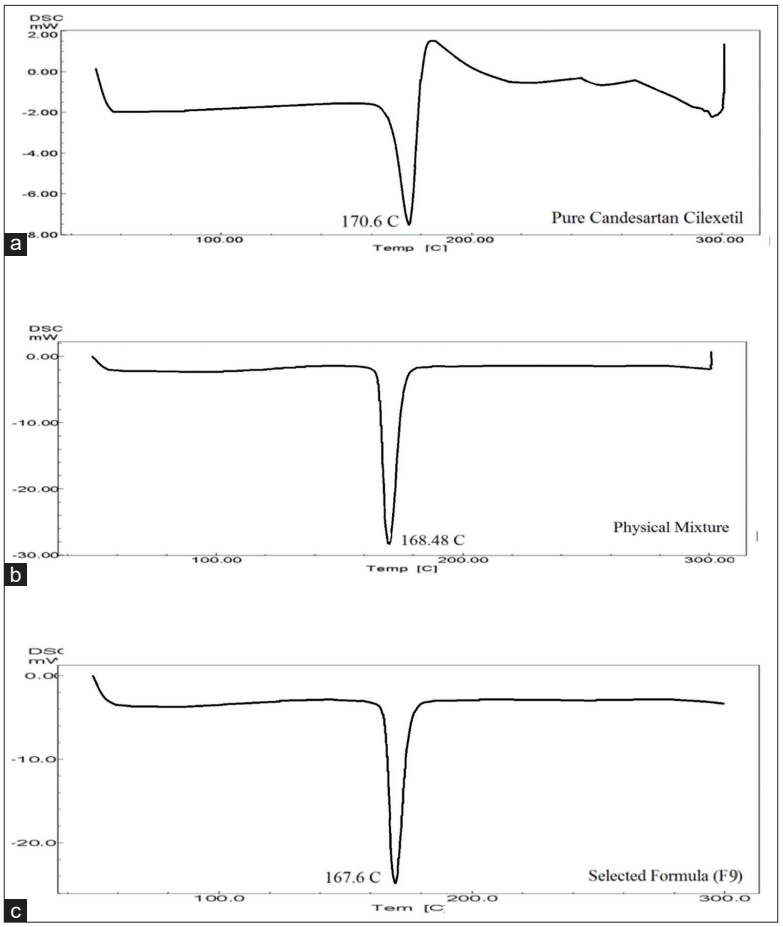

Figure 7: DSC thermograms. (a) Candesartan cilexetil. (b) Physical mixture of starch tartrate. (c) Optimized formulation

Further stability studies according to the ICH guidelines were conducted on F9 formulation. The outcomes of the stability studies indicated that the formulation does not have any huge changes in its physical and chemical properties. The outcomes are shown in Table 9. The drug content did not alter more than 1–2%. There was no huge alteration in medicament content, wetting time, and disintegrating time of CCFDTs even after 3 months; hence, the formulations were found to be stable.

CONCLUSION

The phytochemical composition, physicochemical properties, and toxicological evaluation of prepared starch tartrate proved the safety and possibility of using novel polymer for FDT formulations. The outcomes of pre-compression properties declared the good flow properties of granules. FTIR, DSC studies proved that there is no drug excipient incompatibility within the physical blends of formulations. From the *in vitro* disintegration and dissolution studies, it was clear that the proportion of the superdisintegrant has impressively impacted the disintegration and dissolution properties of different formulations.

Among the investigated superdisintegrants the formulation that contains 5% starch tartrate exhibits rapid disintegration and dissolution profile compared to all other formulation, this may be due to the high capillary nature of the disintegrant and rapid penetration of the buffer medium resulting in the creation of hydrostatic pressure in the tablet bringing about quicker deterioration.[35] Drug kinetics is a valuable characteristic of a formulation in illustrating the drug dissolution profile. Various mathematical models have been introduced from the past few years to examine the drug release from various formulations.[36] The release of drug in optimized (5% starch tartrate) formulation followed Higuchi model, in which the release mechanism is mainly diffusion and concentration acts as a main driving force in drug release.

It was finally concluded that selection of natural polymer such as potato starch provides safety and effective release of drug from the formulation.

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