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Research Article

ENHANCEMENT OF ORAL BIOAVAILABILITY TELMISARTAN FAST-DISSOLVING TABLETS EMPLOYING SWEETSOP STARCH AS A NEW SUPERDISINTEGRANT

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ABSTRACT

Objectives: Telmisartan is a BCS class-II drug with low bioavailability (BA) (42–58%) due to its poor solubility. To enhance the solubility and BA, it can be formulated in fast-dissolving tablets (FDTs) employing sweetsop starch (SSS) as a new natural super disintegrant through a 2^3 factorial design.

Methods: SSS was extracted from the pulp of *Annona squamosa L*. The micromeritic characteristics of SSS were assessed, and the resulting product was utilized as a new super disintegrant in the direct compression method of formulating telmisartan (TSN) FDTs. The SSS was evaluated employing Fourier-transform infrared spectroscopy (FTIR), powdered X-ray diffraction, differential scanning calorimetry (DSC), and scanning electron microscopy. SSS, potato starch, and sodium starch glycolate were employed as superdisintegrants, and factorial design was used to investigate their disintegration property, wetting time (WT), and *in vitro* dissolution. The hardness, friability, homogeneity of drug content, water absorption ratio (R), *in vivo* pharmacokinetics, and stability parameters of formulated TSN FDTs were assessed.

Results: Micromeritic characteristics revealed that the produced SSS was fine, free-flowing, and crystalline. FTIR and DSC investigations indicated that there were no drug-excipient interactions. From the prepared formulations (F1 to F8), the one with a 5% SSS containing formulation TF2 demonstrated 98.44±1% drug release within 10 min with 59±0.14 s, WT and had 42±01 s disintegration time. The optimized formula attained peak plasma concentration extremely quickly and showed 76.05% relative BA.

Conclusion: The formula containing 5% SSS showed good mechanical and physical characteristics, increased drug dissolution, and promoted quick disintegration with enhanced relative BA in the management of hypertension and patient acceptance.

Keywords: Super disintegrant, Sweetsop starch, *In vitro* dissolution, Bioavailability.

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INTRODUCTION

The oral route of administration is the most widely preferred method for both systemic and local drug delivery, and it remains a standard approach in the area of pharmaceutics. This method is recognized for its safety, convenience, patient acceptance, and cost-effectiveness, making it the optimal choice for ensuring patient compliance. However, oral drug delivery systems encounter significant challenges due to the harsh physiological and physicochemical conditions present in the gastrointestinal tract (GIT). These challenges can limit drug bioavailability (BA) and complicate targeted delivery [1,2].

The optimal usage of superdisintegrants remains difficult since they must be able to dissolve in the oral cavity as quickly as feasible [3]. Much research has been conducted on natural superdisintegrants such as starch derivatives (corn and potato starch [PS]), alginates, guar gum, chitosan, and Plantago ovata [4]. Natural superdisintegrants are non-toxic, reduce the risk of adverse reactions, are biocompatible, and are cost-effective, making them suitable for pharmaceutical applications [5].

A literature survey indicated that sweetsop starch has not previously been employed as a superdisintegrant. In this study, we extracted starch from the pulp of sweetsop fruit [6] which requires fewer processing steps and is less expensive, and we utilized it as a supedisintegrant to improve the solubility and dissolution of carvedilol. A comparison will be made using existing marked superdisintegrants and newly synthesized superdisintegrant, i.e., sweetsop starch (SSS).

Telmisartan (TSN), an antihypertensive, belongs to the BCS type II medication that has limited BA [7]. In pharmaceutical research, various methods have been investigated to enhance the dissolution of water-insoluble drugs with water insoluble in fast-dissolving tablets (FDTs), which will provide more rapid and higher absorption than their usual oral dosage forms. This type of tablet reduces the time between drug disintegration and absorption by dissolving it in saliva and absorbing it before it reaches the GIT. Drug absorption often happens in the mouth, throat, and especially the oral cavity. Pregastric absorption improves BA by bypassing hepatic metabolism [8,9].

The present research work discusses the optimization of the telmisartan FDTs using the direct compression method as a new superdisintegrant in enhancing the oral BA of the poorly soluble drug. 2^3 Factorial design was employed to understand the impact of each independent superdisintegrant and the interaction of each other at the levels of 0 and 5 %. Here, SSS (A), PS (B), along sodium starch glycolate (SSG) (C) as independent variables, and disintegration time (DT), wetting time (WT), and % dissolved in 10 min were the independent variables [10].

MATERIALS AND METHODS

Materials

The following ingredients were bought from Molychem in Mumbai: Telmisartan, PS, SSG, microcrystalline cellulose (MCC), mannitol, magnesium stearate, and talc from Yarrow Chem Mumbai, Maharashtra. In the laboratory, SSS was isolated from the pulp of *Annona squamosa* L.

Methods

Isolation of SSS

The sweetsop fruits (*A. squamosa L*., Voucher Number 0194; the botanical specimen was confirmed by a plant taxonomist (IAAT: 337)

were cleaned, the outer layer, the seeds removed, and the pulp extracted. After chopping the pulp into cubes of 5–6 cm, it was quickly washed in a sodium sulfite solution and dried at 50°C. The dried chips were ground in a ball mill for 2 h, and the dry chips were mixed with 5 times their weight in distilled water (DW) and kept aside for 2 h. After passing the mixture through a muslin cloth, the obtained starch milk was centrifuged at 5000 rpm for 0.5 h, and then, decantation of supernatant was done. The resultant starch sediment, which included a thin coating of brown mucus, was mixed with a 0.3% sodium hydroxide (w/v) solution and repeatedly rinsed and centrifuged until we got a pure white starch. The starch was dried and kept in a sealed container [11].

Analysis of SSS characteristics

SSS was assessed for the following properties.

Solubility

The SSS solubility has been measured with aqueous and non-aqueous solvents, including petroleum ether, acetone, dichloromethane, alcohol, and chloroform [12].

Viscosity

A 4% w/v aqueous dispersion of SSS has been analyzed using a viscometer (Ostwald).

Swelling index (SI)

1 g of SSS was taken into 2 graded test tubes, one was filled with light paraffin, and the second one was added with DW. The dispersions were kept aside for 12 h. Sediment volumes of the tubes are noted. The SI of the material has been computed utilizing the following formula:

$$S.I\,(\%) = \frac{\textit{Volume of sediment in water} - \textit{volume of sediment in light liquid paraffin}}{\textit{Volume of sediment in light paraffin}} \times 100$$

pH

Using a digital pH meter, 1.0% w/v suspensions of SSS were analyzed in triplicate, and the findings were noted.

Density

The density (g/cc) of an SSS dispersion in DW has been analyzed with the liquid displacement method. Benzene was used as the displacing liquid.

PS

This analysis was performed by sifting through standard sieves.

Moisture absorption

When handling, storing, and combining SSS into different formulations, especially in culinary and medicinal applications, moisture absorption is an important feature to consider. The final product's effectiveness and shelf life can be strongly impacted by the moisture content. To preserve the quality and functionality of SSS in various applications, it is imperative to maintain the ideal moisture level. The moisture absorption has been evaluated using a desiccator at 25°C, retaining a relative humidity of around 84%.

Bulk density (BD)

BD was determined using 50 times tapping in a graduated cylinder, and the results were calculated accordingly [13].

$$D = \frac{\text{Mass of a powder}}{\text{True volume of a powder}}$$

$$TD = \frac{\text{Mass of a powder}}{\text{Tapped volume of a powder}}$$

Measurement of powder flow

It was determined using the set funnel method. The formula below calculates the angle of repose.

$$\tan\theta = \frac{h}{r}$$

$$\theta = tan^{-1}\frac{h}{r}$$

θ=angle of repose; h=height of pile; r=radius of pile.

Compressibility index (CI)

The CI was found through measurement of the beginning volume (V_0) and concluding volume (V) after subjecting a sample of SSS to one hundred tapings in a tube. It was then noted using the following equation [14].

$$(CI) = \frac{V_0 - V}{V} \times 100$$

Estimation of ash content

The isolated starch has been heated to a temperature that evaporates the organic chemical and their derivatives, resulting in mineral elements of minerals along with inorganic compound residues. The percentage of ash must be <1% [15].

ASH (%)=([ashed wt.] - [crucible wt.]) × 100/([crucible and sample wt.] - [crucible wt.])

Estimation of loss on drying (LOD)

A single gram of powdered SSS was measured and placed in a preheated assessing jar with a cover. It was then dried in an oven at 105°C until a consistent weight.

Identification test: Iodine test

The SSS solution was treated with a solution of potassium iodide with iodine in water. Then, it turns out into a bright blue-black color that indicates the existence of starch [16].

Analysis of the amount of amylose

The amount of amylose in isolated starch has been determined using Juliano's (1971) technique, with slight changes. Pure amylose (40 mg) had been added to a test tube holding 1 mL of 95% ethanol along with 9 mL of sodium hydroxide, 1N. The sample in the tube had been heated in boiling water for over 10 min, generating a gel, then cooled. The resultant gel (1, 2, 3, 4, and 5 mL) is transferred to five 100 mL-volumetric flasks and treated using 0.2, 0.4, 0.6, 0.8, as well as 1 mL of acetic acid 1N, respectively. Each volumetric flask with a capacity of 100 mL was then filled with 2 mL of iodine solution, with enough DW. The accomplished mixture is agitated to get homogeneous and then kept aside for 20 min. Then analyzed utilizing a ultraviolet-visible (UV-Vis) spectrophotometer at 620 nm. The amount of amylose in the sample was calculated by interpolating the sample's absorbance value with a linear calibration curve, employing equation [16].

$$\%\ \text{Amylose}\,(x) = \frac{(\text{absorbance} - \text{y intercept})}{(\text{slope})} \times 1$$

Drug-excipient compatibility

Fourier transform infrared spectroscopy (FTIR)

The IR spectrum for SSS has been obtained from samples made with an FTIR device (Tokyo, Japan) (BRUKER) in potassium bromide. Then, it was produced in KBr disks at a pressure of six to eight tons using a hydrostatic press. FTIR analysis was employed to evaluate the

Table 1: Formulae of TSN FDTs

Ingredient (mg per tablet)	F1	F2	F3	F4	F5	F6	F7	F8
TSN	40.0	40.0	40.0	40.0	40.0	40.0	40.0	40.0
SSS	---	10.0	---	10.0	---	10.0	---	10.0
PS	---	---	10.0	10.0	---	---	10.0	10.0
SSG	---	---	---	---	10.0	10.0	10.0	10.0
MCC	112.0	112.0	112.0	102.0	112.0	102.0	102.0	92.0
Mannitol	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0
Talc	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Magnesium stearate	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Total tablet weight	200.0	200.0	200.0	200.0	200.0	200.0	200.0	200.0

SSS: Sweetsop starch, PS: Potato starch, SSG: Sodium starch glycolate, MCC: Microcrystalline cellulose, FDTs: Fast-dissolving tablets

compatibility between SSS and TSN. TSN's FTIR and its 1:1 mixture with SSS and TSN were recorded [17].

Differential scanning calorimetry (DSC)

DSC measurements of TSN, TSN with SSS (1:1) are performed using a Perkin Elmer thermal analyzer that had a heated temperature range between 50 and 300°C with a rate of heating of 10°C/min [18].

X-ray diffractometry (XRD)

The diffraction pattern of SSS has been obtained using an XRD (Analytical Spectra's Pvt. Ltd., Singapore). It took place at the ambient temp (30°C) using a diffractometer; target, Cu (λ 1.54 A), filters, Ni; voltage, 40 kV; power 30 mA; scanned rate 4°/min; and recorded between 30 and 150° with the full scale 200 [19].

Morphology by scanning electron microscope (SEM)

The morphology of SSS was observed using an SEM. Scanning electron micrographs of isolated starch samples sputtered using gold to a layer thickness of approximately 30 nm (Sputter Coater Type E 5100, Biorad GmbH, Munich, Germany) were obtained at ×5000 magnification using a DSM 940 equipment (Carl Zeiss, Oberkochen, Germany). The accelerating voltage ranged from 0.3 to 40 kV. The granule size was calculated using the validated scale bar on the SEM image [20].

Preparation of TSN FDTs

Direct compression has been used in the preparation of the tablets. Table 1 displays the ingredients of the various fast-dissolving TSN tablet formulations. Before combining, each ingredient was run through a #100 mesh filter to guarantee uniformity in the particle size. TSN was mixed with a mortar and pestle after SSS, SSG, PS, mannitol, and MCC were carefully measured out and blended. Finally, the powder has talc and magnesium stearate added to it. The tablets were finally prepared using a rotary press with eight stations [21].

The optimization technique

To optimize the formulation variables 2^3 factorial design was used, a total of 8 runs were generated using the Design Expert® software. Table 2 illustrates detailed information on the investigated response variables and the design matrix. These choices of concentrations were based on preliminary studies conducted before setting up the experimental design. SSS, PS, and SSG as superdisintegrants are the independent variables, and WT, DT, and percent drug dissolved in 10 min (PD10) are response variables (dependent variables) [22].

Evaluation of TSN FDTs

Hardness

This was assessed using a Monsanto hardness tester, and the force was measured in kilograms (kg). Hardness values were determined for three tablets from each formulation.

In analysis, (Monsanto tester), measures force in kilograms per centimeter and needs force to be delivered to the tablet diametrically using an integrated spring.

Table 2: Formulation composition constraints of TSN FDTs

Parameter	Low (−1)	High (+1)	Constraints
A: SSS	0	5	
B: PS	0	5	
C: SSG	0	5	
Dependent variables			
Y1: WT (s)			Minimize
Y2: DT (s)			Minimize
Y3: PD in 10 min (%)			Maximize

SSS: Sweetsop starch, PS: Potato starch, SSG: Sodium starch glycolate, WT: Wetting time, DT: Disintegration time, PD: Percent dissolved in 10 min

Uniformity of weight

Twenty pills were the subject of a weight variance investigation, which comprised calculating the actual weight difference between the tablets and their average weight.

Friability

A Roche friabilator was used to evaluate the tablets' friability. The tablets were turned 100 times around at a speed of 25 revolutions/min for 4 min. The pills were weighed again after the penalties were removed, and the % of weight reduction was computed [23].

$$F = \frac{W_{(initial)} - W_{(final)}}{W_{(initial)}} \times 100$$

Drug content (DC)

Ten tablets were ground into powder for the content uniformity test. A volume of powder equal to 10 mg of TSN was then extracted and filtered into a pH 6.8 buffer. Spectrophotometric absorbance measurement following appropriate dilution with buffer was used to quantify the TSN concentration.

WT

A petri dish of the same diameter was filled with five circular tissue sheets, each measuring 0.1 m in diameter. Ten mL of aqueous medium, including amaranth (water-soluble dye), was poured onto the plate. The FDTs were then carefully kept on a tissue sheet. The time elapsed until water fully covered the top of the tab is referred to as the WT [24].

Water absorption ratio (R)

6 mL of water and a piece of tissue paper folded twice were put on a tiny plate. After placing the tablet on tissue paper, it was fully saturated and it was then reweighed. The R is calculated using the equation below.

$$R = \frac{100\,(W_a - W_b)}{W_a}$$

Where, W_a=Weight of tablet after water absorption, W_b=Weight of tablet before water absorption.

In vitro DT

Using a pH 6.8 buffer and USP disintegration equipment, the DT of FDTs was determined. The temperature was 37±0.2°C and the buffer volume was 900 mL. The time taken for the complete DT of six tablets was noted, and the mean DT was noted [25].

In vitro dissolution

The *in vitro* dissolving rate investigation of TSN-FDTs requires the use of dissolution test equipment (electrolab TDT-08 L). The dissolving medium was the 900 mL pH 6.8 buffer with dissolution test equipment (electrolab TDT-08L). At prearranged intervals, 5 mL of the sample was obtained and replaced with buffer, purified, and analyzed with a T360 UV/Vis double-beam spectrophotometer at 242 nm. The cumulative percent has been noted. Each test was conducted three times (n=3) [26].

Stability studies

The International Council for Harmonisation and World Health Organization recommend that an optimum composition of fast-dissolving carvedilol tablets should be subjected to expedited testing, which can be achieved by simply storing the tablets in HDPE containers for 6 months at a temperature of 40°C and 75° RH. The physical changes and dissolution properties had been evaluated both during and after their 6-month storage.

In vivo pharmacokinetic studies

The Institutional Animal Ethics Committee approved the experimental protocol (approval number: AKRGCP/Pheuc/2021–3). 3 male Wistar rats 200–250 g (Procured from Jeevan Life Sciences, Malkajgiri, Hyderabad) were housed in cages. They also experienced a daily cycle of 12 h of light and 12 h of darkness. Randomly selected rats were divided into two batches, each containing six rats. One group was given a pure drug (4.13 mg/kg body weight), and another group was given the F2 formulation (4.13 mg/kg body weight). All groups received different treatments. The rats were given a 12-h restriction before the study began, and during that time, food and water were only periodically available to them. The dose was given to the wiser rats using a catheter. After the rats were given the drug, they were given moderate ether anesthesia. At predefined intervals, blood was extracted. The blood plasma samples are centrifuged at 5000 rpm and kept at −20°C. The samples were assessed using a well-known high-performance liquid chromatography (Shimadzu LC) approach to look into the pharmacokinetic information [27].

Table 3: The sweetsop starch's physical and micromeritic characteristics

Parameter	Observation (%)
Solubility	In soluble in all tested organic and aqueous solvents
Iodine test	Bluish violet color - presence of starch
pH (1% aqueous dispersion)	4.88±0.02
Viscosity (4%w/v aq. dispersion)	317±0.005 cps
LOD	10.27±0.07
Content of ash	0.92±0.14
SI	74±0.04
Moisture absorption	6.4±0.6
Content of amylose	24.44±0.04
CI	14.11±2
BD	0.545±0.063 g/cc
Angle of repose	26.38°±2.34
TD	0.505±0.03 g/cc
Particle size	5.2±3.2 µm

LOD: Loss on drying, SI: Swelling index, CI: Compressibility index, BD: Bulk density, TD: Tapped density. *n=3, Mean±standard deviation

Statistical analysis

Analyzed using one-way analysis of variance was employed with a 95% confidence level to determine the significance of differences among groups. Significant differences were further analyzed using the *post hoc* Duncan test to identify specific variations between test groups [28].

RESULTS AND DISCUSSION

The SSS that was produced was a fine, crystalline powder. The SI of 74% indicated that water caused SSS to expand significantly. It was discovered that the SSS BD and tapped density were, respectively, 0.545 and 0.505 g/cc. Ash content of SSS was found to be 0.92±0.14%, amylose content was 24.44±0.04%, and LOD was 10.27±0.07%. Moisture absorption was found to be 4.4±0.6%, and the angle of repose was 26.38°±2.34. These results indicated that isolated SSS having good SI and flow properties are essential for FDTs. Due to its crystalline nature and physical properties resembling those of a superdisintegrant (Table 3), it was suggested that SSS could serve as a new natural superdisintegrant in the manufacturing of FDTs.

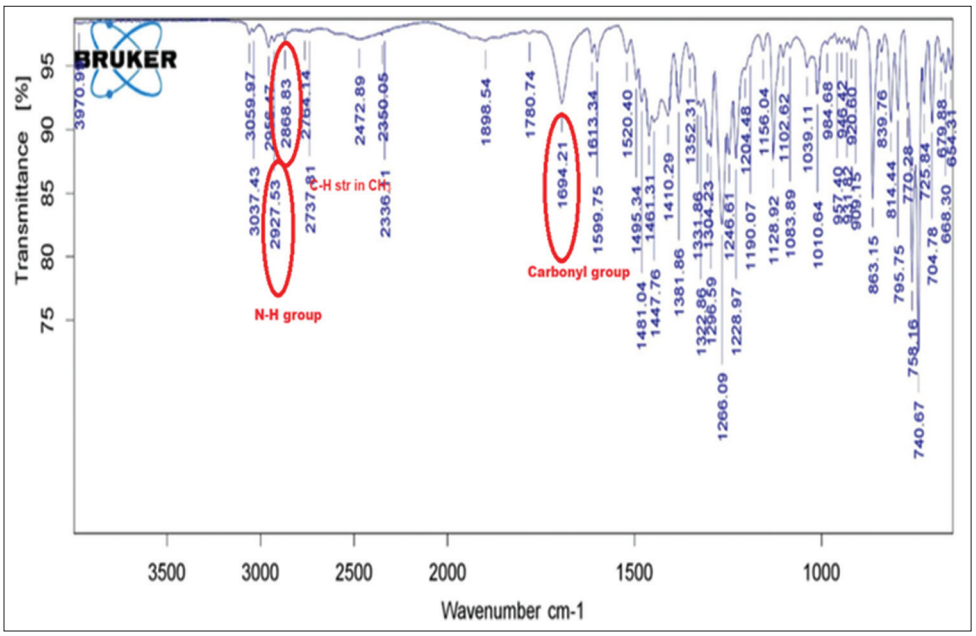

Fig. 1: TSN Fourier-transform infrared spectroscopy spectrum

Drug excipient compatibility studies

The C-N stretching resonance at 1296.59 cm^{-1}, the CH_3 bending at 1447.76 cm^{-1}, the C-C aromatic bending at 1599 cm^{-1}, the C-H bending vibrations at 1461.31 cm^{-1}, the carbonyl stretching vibration at 1694.21 cm^{-1}, the N-H stretching at 2955.80 cm^{-1}, and the C-H stretching at 2868.83 cm^{-1} were among the distinctive peaks visible in the telmisartan infrared (IR) spectra (Fig. 1).

The propyl group's C-H stretching was visible in the SSS (Fig. 2) IR band at 1337 cm^{-1}, whereas the bending vibration of CH_2 was identified as the cause of the band at 1417 cm^{-1}. The bending vibration of H-O-H is shown in the IR band at 1640 cm^{-1}. The symmetric stretching of H-C-H was the cause of the band at 2928 cm^{-1}. The stretching of the methyl group created by hydroxy propylation, both symmetrically and asymmetrically, was identified as the cause of the IR band at 2359 cm^{-1}. The hydroxy group of the original starch structure is represented by the broad IR band at 3343 cm^{-1}, while the hydroxy group of the propylated starch is represented by a medium-sharp peak at 3896 cm^{-1}. Ether bond (C–O) stretching is represented by the prominent peak at 1012 cm^{-1}.

The FTIR results of TSN-SSS (Fig. 3) indicated that there was no interaction between the novel superdisintegrant SSS and the chosen medication. Therefore, SSS can be utilized as a superdisintegrant in the formulation of FDT-containing TSN.

The existence of distinct diffraction peak locations at 14.9, 19.3, and 22.8, along with a doublet spanning from 16.8 to 17.8, indicates that the SSS is crystalline. The crystalline polymorph structure depicted in Fig. 4 is responsible for the patterns that have been noticed. SSS granules appeared polygonal in form and ranged in size from 2 to 5 µm. The starch particle form in Fig. 5 seemed to range from irregular to spherical.

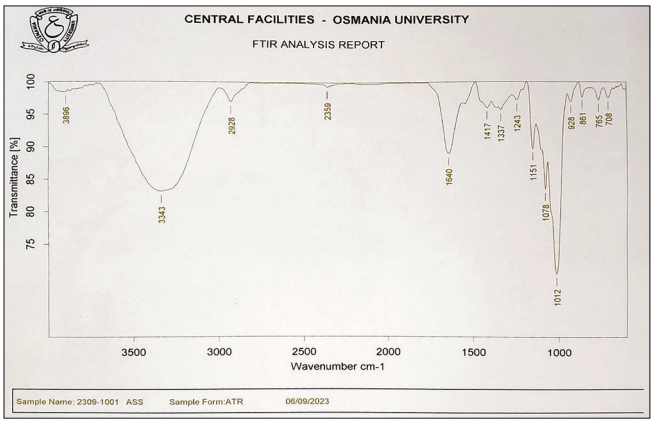

Fig. 2: Fourier-transform infrared spectroscopy spectrum of sweetsop starch

The DSC thermogram of telmisartan-SSS also shows a prominent endothermic peak at 272.47 K. The DSC thermogram of pure telmisartan exhibits a noticeable endothermic curve at its melting point of 271.56 K. It was clear from the peaks in this region that SSS did not interact with the telmisartan medication, as it falls between 267 and 273 K, which is the melting point of the drug. Figs. 6 and 7 display the DSC of pure TSN along with TSN-SSS.

Evaluation test

Hardness

The tablets ranged in hardness from 3.8±0.001 to 4.0±0.001 kg/cm^2. It suggests a high level of adaptability and the capacity to manage stress that arises from different sources. The tablets' hardness was higher than that of the tablets made in compliance with Jaya and Amala, which has a hardness of 3.5 kg/cm^2 [29].

Friability

It was found that the weight loss was <0.17%, demonstrating the tablets' strong mechanical resilience. The friability findings (<0.17%) were best to withstand the mechanical shocks compared to the tab manufactured by Dhahir and Al-Kotaji which has a friability of 0.8% [30].

DC uniformity (DCU)

The medication content of all manufactured FDTs ranged from 37.11±0.12 to 39.88±0.46 mg of TSN, under the recommended DCU.

Water absorption ratio and WT

The definition of constraints and criteria for FDT was found to be met by the *in vitro* WT of the carvedilol FDT prepared with 5% of SSS as a superdisintegrant (Fig. 8). Table 4 displays a WT for the formulations. WT of the best formulation was found to be 59±0.14 s. The WT was shorter than the tablets made by Sharma *et al*., it has a WT of 70±8 s [31]. The water absorption ratio of 74±0.03% was observed in the optimized formulation F2 of TSN FDT.

In vitro DT

Table 4 indicates that the DT of all tablets ranged from 36.0±02 to 650±01 s. The optimal formulation F2 had a DT of 42±02 s. The

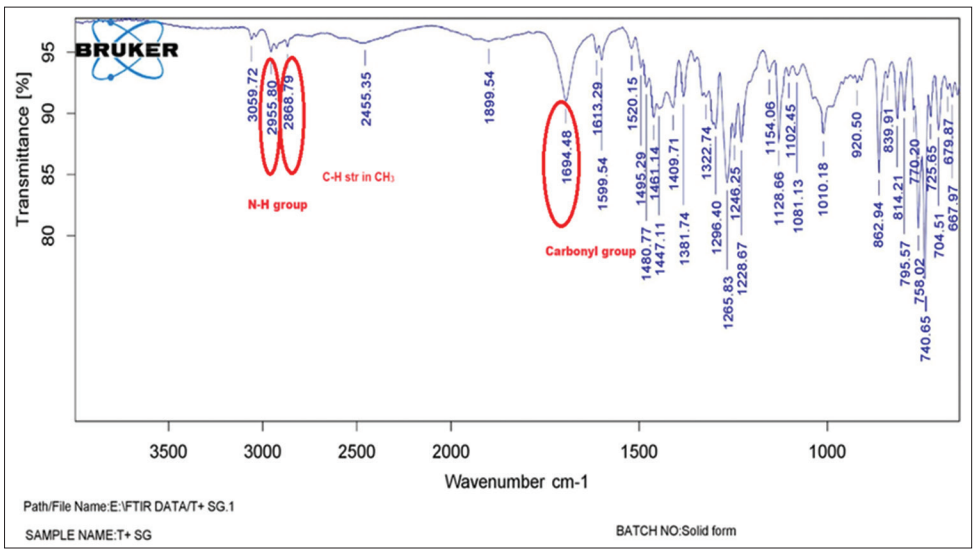

Fig. 3: Fourier-transform infrared spectroscopy spectrum of TSN with sweetsop starch

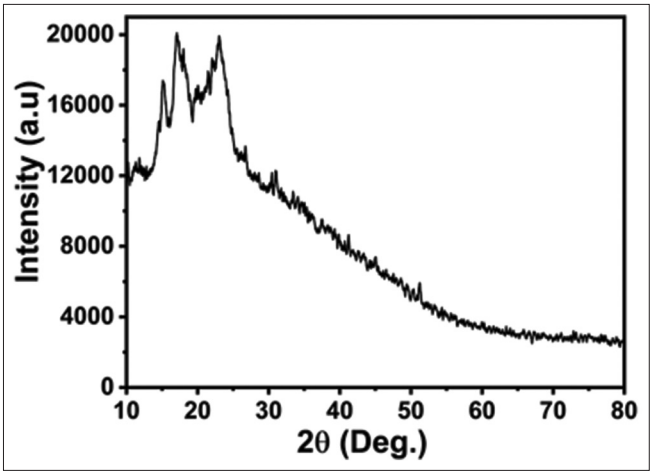

Fig. 4: X-ray diffractometry of sweetsop starch

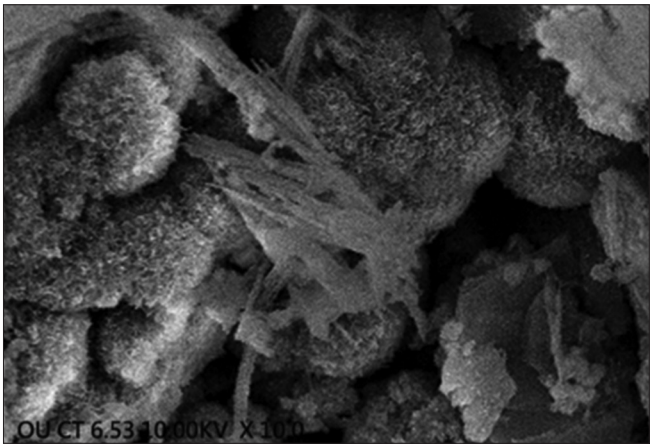

Fig. 5: Scanning electron microscope image of sweetsop starch

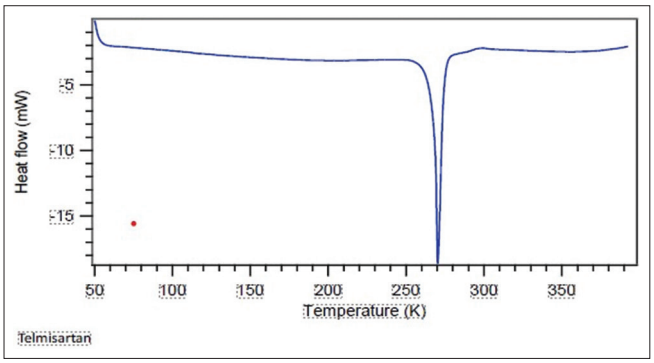

Fig. 6: Differential scanning calorimetry of TSN

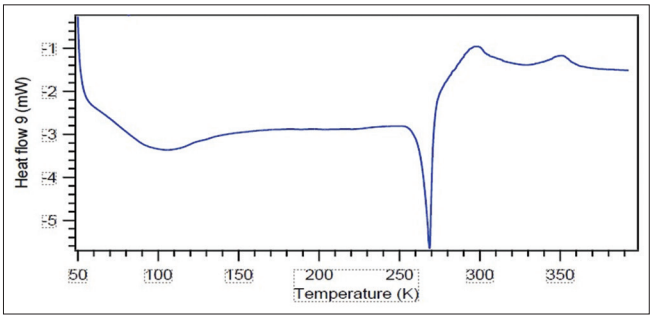

Fig. 7: Differential scanning calorimetry of TSN with sweetsop starch

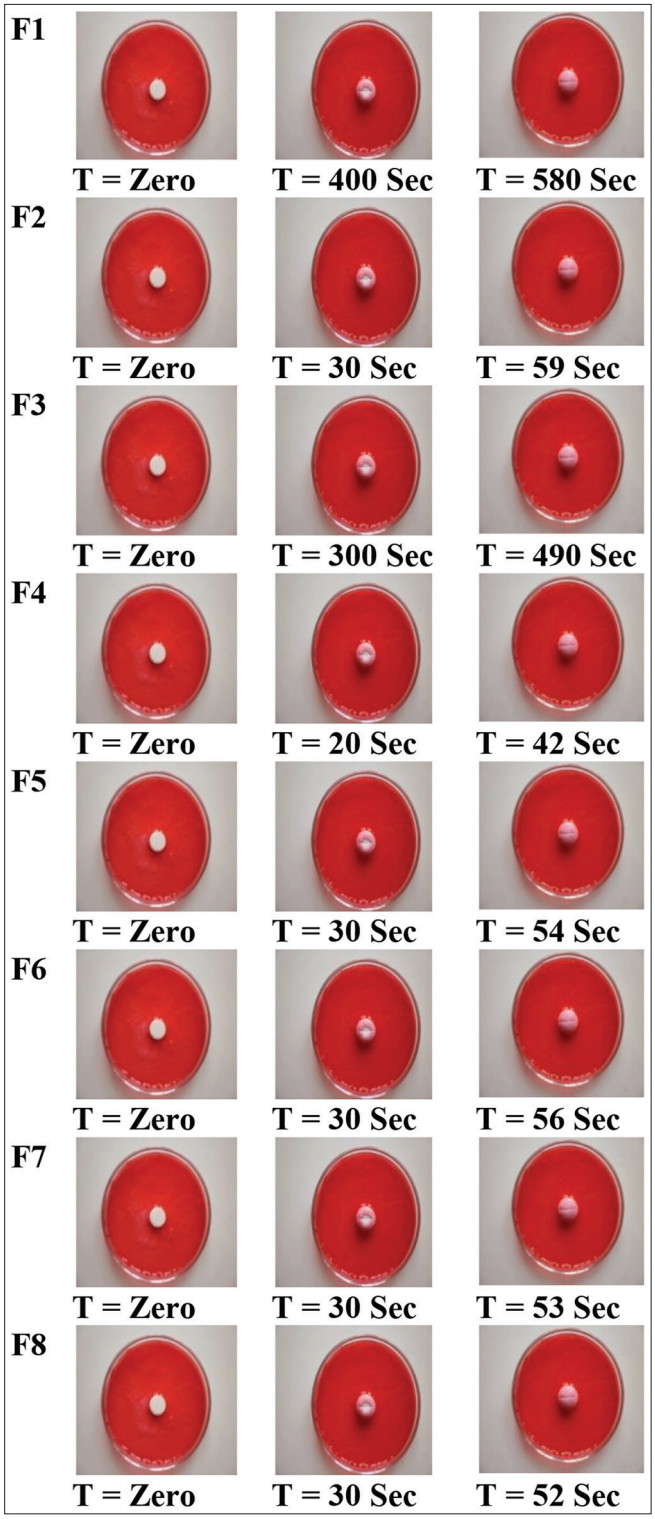

Fig. 8: Wetting time of telmisartan fast-dissolving tablets made with sweetsop starch

concentration of the superdisintegrant was inversely proportional to the DT. The best formulation DT was compared to the tablets prepared per Parfati *et al*. and had a DT of 42±02 s [32].

In vitro dissolution studies

Fig. 9 shows the results of *in vitro* dissolution investigations of FDTs containing TSN with SSS (F-1 to F-8). The results indicate that SSS, as a novel superdisintegrant, is effective for formulating fast-dissolving TSN tablets. The optimized formulation, F2, achieved a drug release

Table 4: Post-compression parameters of TSN FDTs

F. no	Hardness kg/cm²	Friability (%) ±SD	Drug content (mg/tab) ±SD	DT (s)±SD	WT (s)±SD	Water absorption (%)±SD
F1	3.8±0.001	0.11±0.014	37.11±0.0.12	650±01	580±0.22	31.41±0.02
F2	4.0±0.001	0.12±0.047	39.88±0.46	42±02	59±0.14	74±0.03
F3	3.9±0.004	0.15±0.055	37.91±0.15	530±02	490±0.21	60±0.02
F4	3.8±0.031	0.12±0.054	38.12±0.14	58±03	42±0.36	78±0.04
F5	3.8±0.041	0.13±0.033	39.47±0.54	52±01	54±0.41	75±0.21
F6	3.9±0.032	0.14±0.047	38.89±0.77	41±02	56±0.24	76±0.33
F7	3.8±0.041	0.16±0.065	39.65±0.98	56±01	53±0.21	78±0.21
F8	3.9±0.022	0.17±0.014	39.74±0.41	36±02	52±0.55	85±0.11

DT: Disintegration time, WT: Wetting time, SD: Standard deviation. *n=6, mean±standard deviation, for drug content n=10, mean±standard deviation

of 97.54±1% in 10 min, which is significantly higher compared to the tablets prepared by Preeti *et al*., which had a 92.46% release in 1 h [25].

Factorial design

WT, DT, and PD10 are response variables (dependent variables) that have been analyzed using the polynomial regression technique, with the independent variables, such as superdisintegrants such as SSS (A), PS (B), and SSG (C). Equations 1, 2, and 3 provide the polynomial equations for WT, DT, and PD in 10 min, respectively.

Wetting time=173.25+121.00A+14.00B+119C−8.75AB−121.25AC−12.75BC+9.50ABC (R^2=1.000) (1)

Percent Drug dissolved in 10 min=69.62+24.29A+6.39B−15.09C−5.59AB−14.72AC+1.78BC+3.02ABC (R^2=1.000) (2)

Disintegration time=183.12+138.88A+13.13B+136.88C−15.88AB−131.12AC−12BC+ 18.13ABC (R^2=1.000) (3)

The meaning of the R^2 indicates which suit is correct. An inference may be drawn using polynomial calculations by evaluating the variable's magnitude and statistical significance (positive or negative).

Using Design Expert 7.11 software, surface response curves and contour plots (CP) were created after the equation was generated. The proportions of each ingredient and their resulting interdependencies with WT, DT, and PD10 are compared in this equation. The accompanying Table 5 shows the relationship between the superdisintegrants SSS (A), PS (B), and SSG (C), as well as how these interactions affect the PD in 10 min, WT, and DT and formulations show no significant differences ($p>0.05$).

CP and SRP were made based on the interplay of effects on the WT, DT, and PD10. Figs. 10-18 display the SRP and CP of the effect of various independent variables' responses on DT, WT, and PD10. CPs of WT, DT, and PD10 are linear. RSP and CP demonstrate the impact of superdisintegrant concentration on WT, DT, and PD10. Plots indicate that the superdisintegrant percentage ranges from 4 to 5%, which lowers the tablet's DT, WT, and enhanced PD10. The concentration of superdisintegrant is inversely related to WT and DT and directly proportional to PD in 10 min.

Table 6 displays the correlation between the superdisintegrant concentration and the WT, DT, and PD10.

Optimized formula

With a 5% concentration of SSS, formulation F2 demonstrated a shorter DT, a higher PD10, and shorter WT. Formulation F2 is similar to formulation F8. Formulation F2 has a single superdisintegrant, SSS, in a concentration range of 5%. F2 is therefore seen as an optimized formulation that was more cost-effective. These results suggest that a single superdisintegrant formulation with an optimal concentration of SSS can effectively enhance the dissolution profile of TSN-FDTs. The ability of SSS to achieve a high percentage of TSN dissolved within 10 min is particularly noteworthy and underscores its potential for developing FDTs. From the response surface plot and CP, it was concluded that the WT and DT plots are linear with an inverse relation to the superdisintegrant concentration. PD10 of RSP and CP indicates that the superdisintegrant concentration is directly proportional and the best concentration was identified to be 4–5%.

Table 5: Superdisintegrants' interactions and their impact on WT, DT, and PD10

Superdisintegrants' Interactions	Effect on		
	WT	DT	PD10
SSS×PS (AB)	-	-	-
SSS×SSG (AC)	-	-	-
PS×SSG (BC)	-	-	+
SSS (A)	+	+	+
PS (B)	+	+	+
SSG (C)	+	+	+
SSS×PS×SSG	+	+	+

DT: Disintegration time, WT: Wetting time, PD10: Percent drug dissolved in 10 min, SSS: Sweetsop starch, PS: Potato starch, SSG: Sodium starch glycolate. "-" signifies a detrimental impact, whereas "+" signifies a beneficial impact

Table 6: Relation between concentration of superdisintegrant on WT, DT, PD10

The interactions among ABC	Relation founded			Recommended ratio (%)
	DT	WT	PD10	
SSS X PS (AB)	Linear	Linear	Linear	4–5
SSSXSSG (AC)	Linear	Linear	Linear	4–5
PSXSSG (BC)	Linear	Linear	Linear	4–5

DT: Disintegration time, WT: Wetting time, PD10: Percent drug dissolved in 10 min, SSS: Sweetsop starch, PS: Potato starch, SSG: Sodium starch glycolate

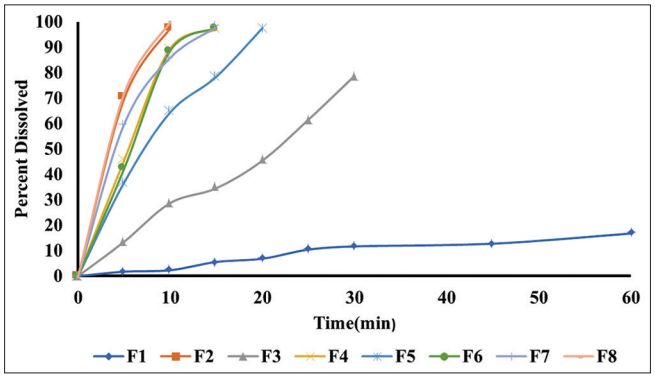

Fig. 9: Dissolution profiles of TSN fast-dissolving tablets (F1-F8)

Pharmacokinetic data analysis

For pharmacokinetic studies, the plasma concentration versus time profile obtained is shown in Fig. 19 and Table 7. Pharmacokinetic parameters, including T_{max}, C_{max}, area under the curve, BA, rate of elimination (K_e), and rate of absorption constant (K_a), were calculated from the plasma profile using MS Excel. The telmisartan plasma

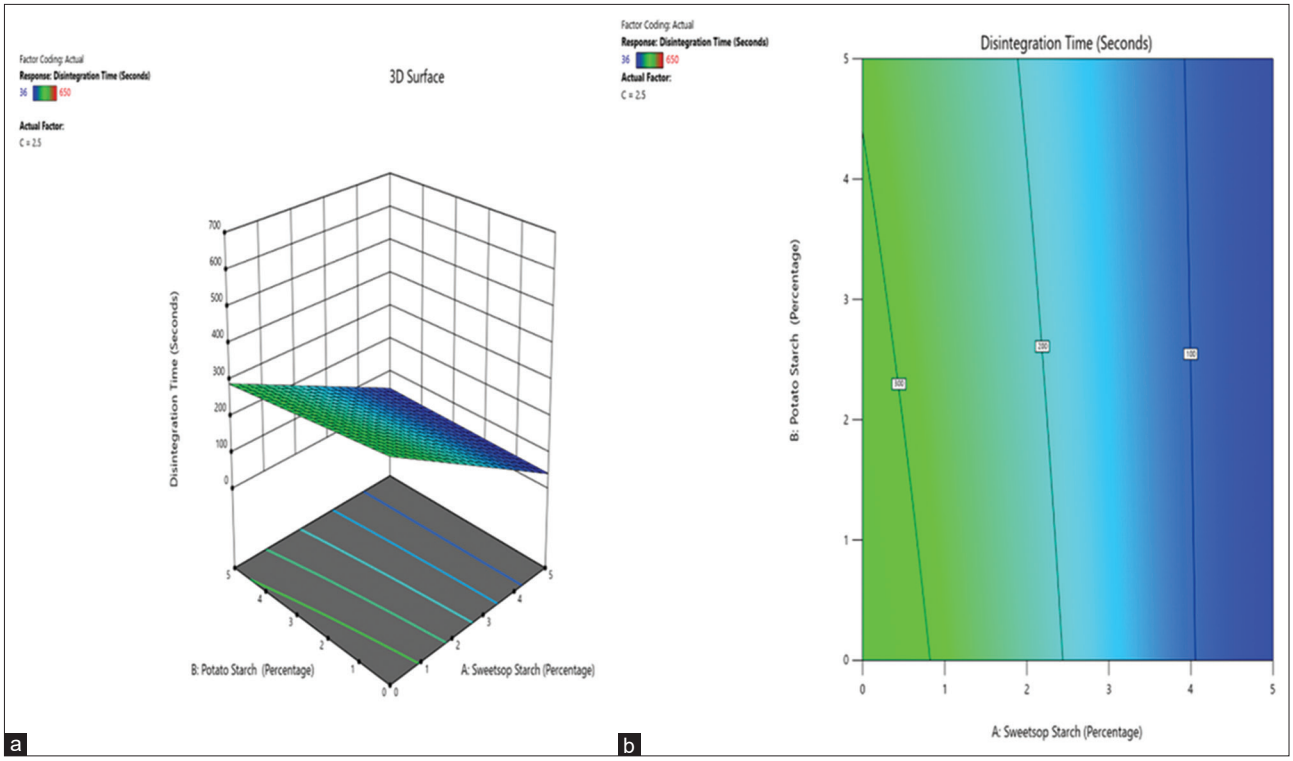

Fig. 10: (a) RSP, (b) contour plots of telmisartan fast-dissolving tablets (effect of sweetsop starch and potato starch on the disintegration time)

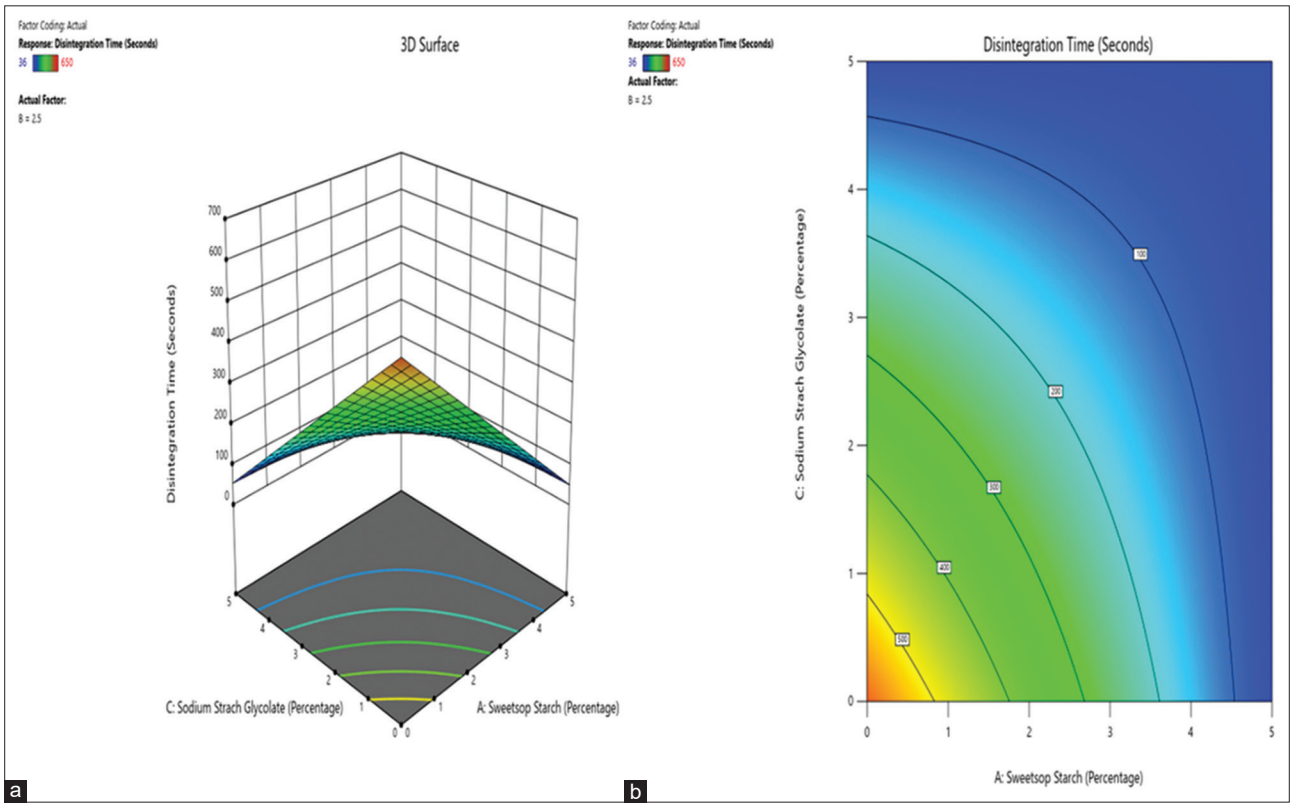

Fig. 11: (a) RSP, (b) contour plots of telmisartan fast-dissolving tablets (effect of sweetsop starch and sodium starch glycolate on the disintegration time)

concentration after the oral administration of pure form of drug (A) and optimized fast dissolving tablets (B). From the plot, it can be concluded that after administration of FDTs of telmisartan, the plasma concentration is higher initially within a short period and attains its C_{max} concentration within 1 h. These results agreed with the results obtained by Devi and Santosh.

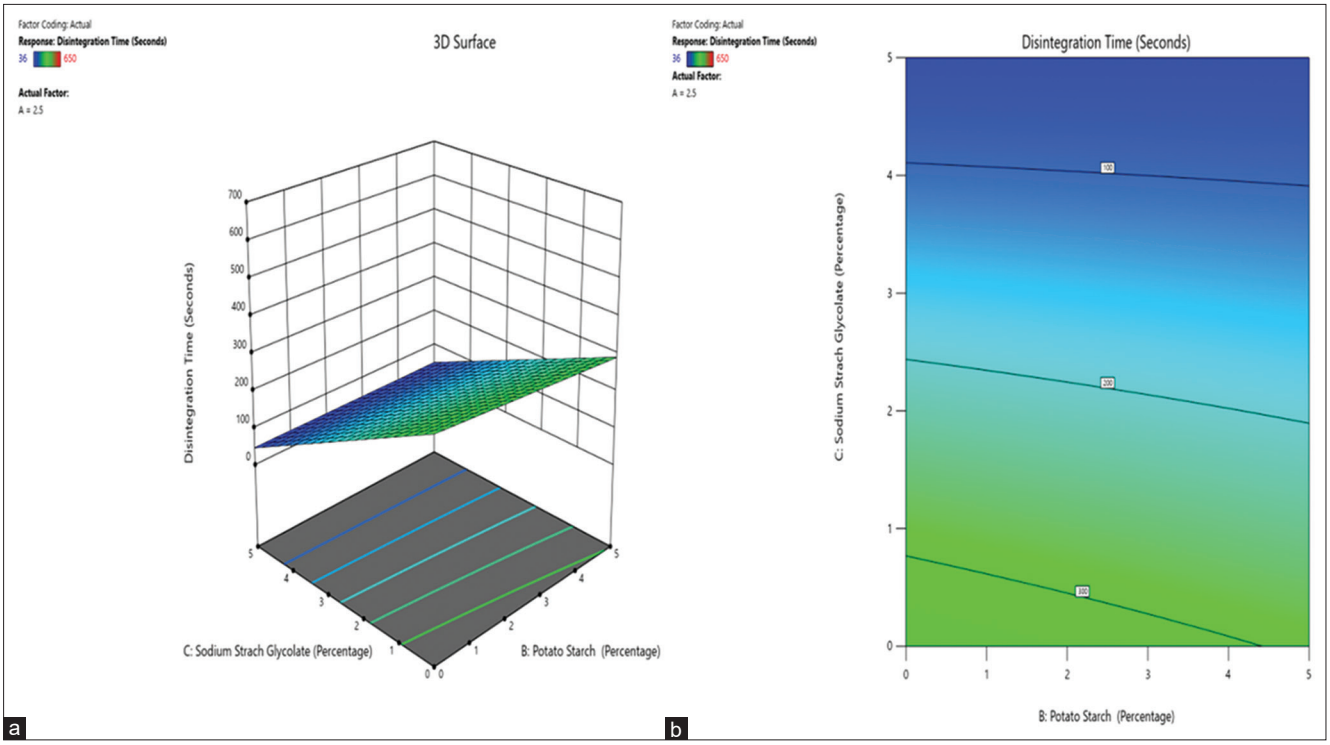

Fig. 12: (a) RSP, (b) contour plots of telmisartan fast-dissolving tablets (effect of potato starch and sodium starch glycolate on the disintegration time)

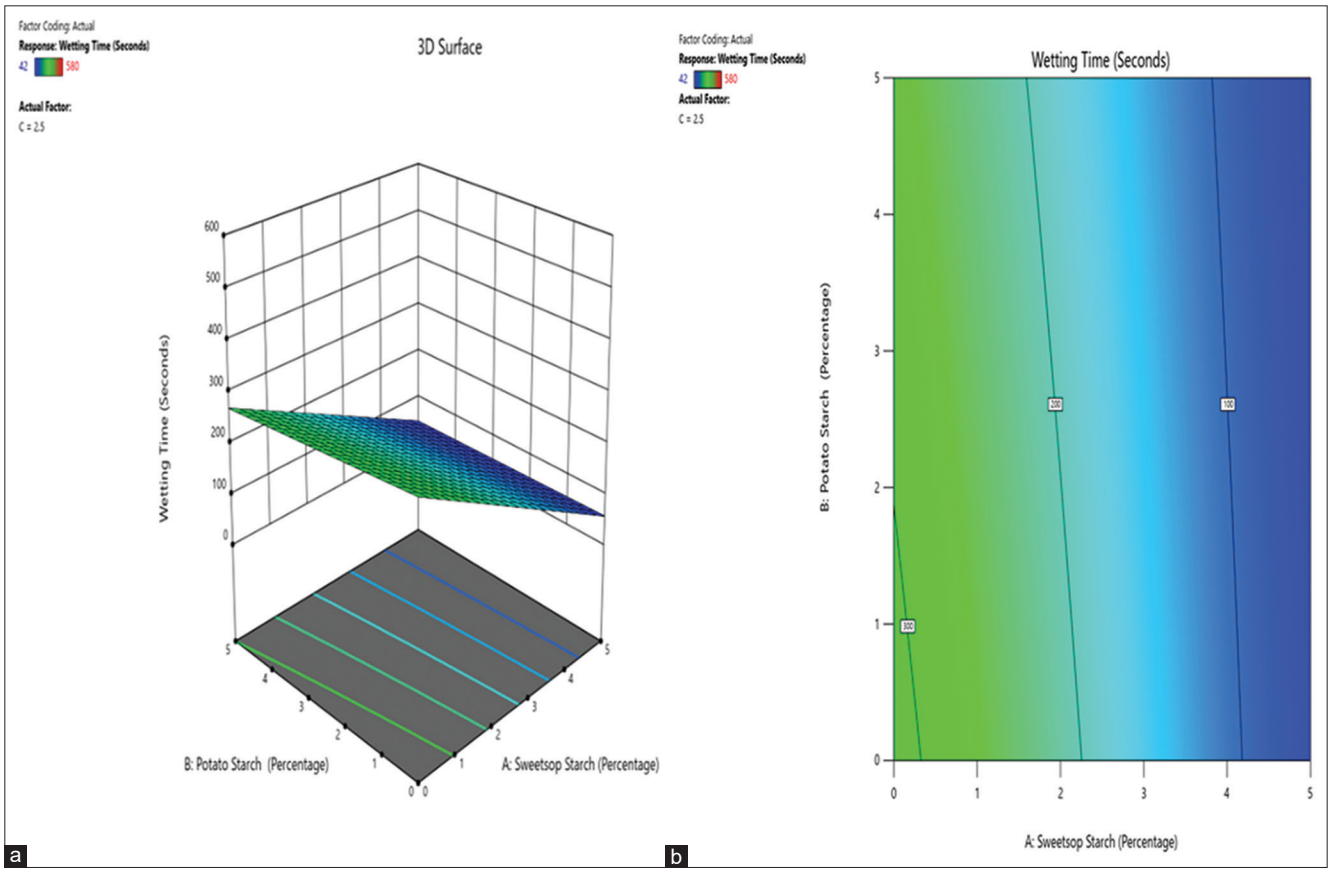

Fig. 13: (a) RSP, (b) contour plots of telmisartan fast-dissolving tablets (effect of sweetsop starch and potato starch on the wetting time)

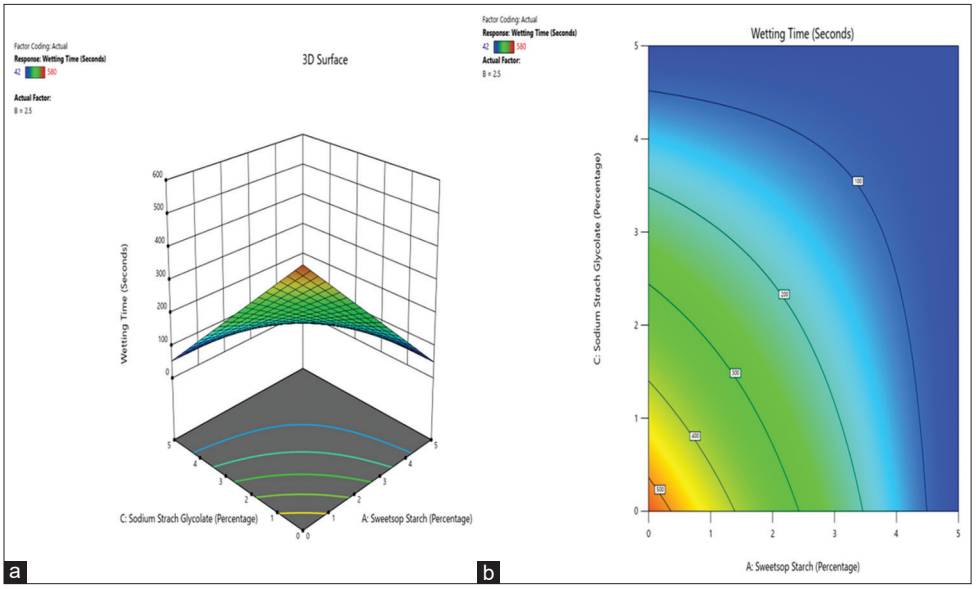

Fig. 14: (a) RSP, (b) contour plots of telmisartan fast-dissolving tablets (effect of sweetsop starch and sodium starch glycolate on the wetting time)

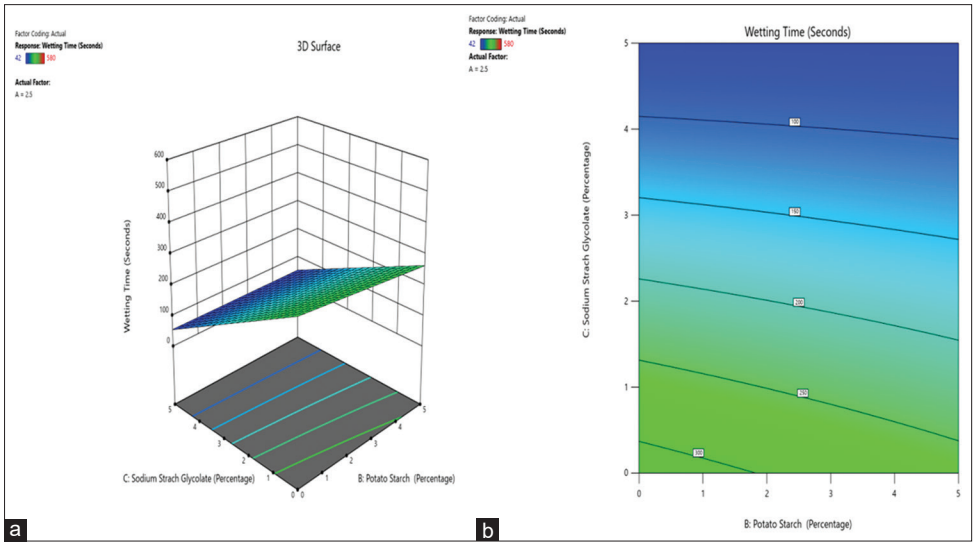

Fig. 15: (a) RSP, (b) contour plots of telmisartan fast-dissolving tablets (effect of potato starch and sodium starch glycolate on the wetting time)

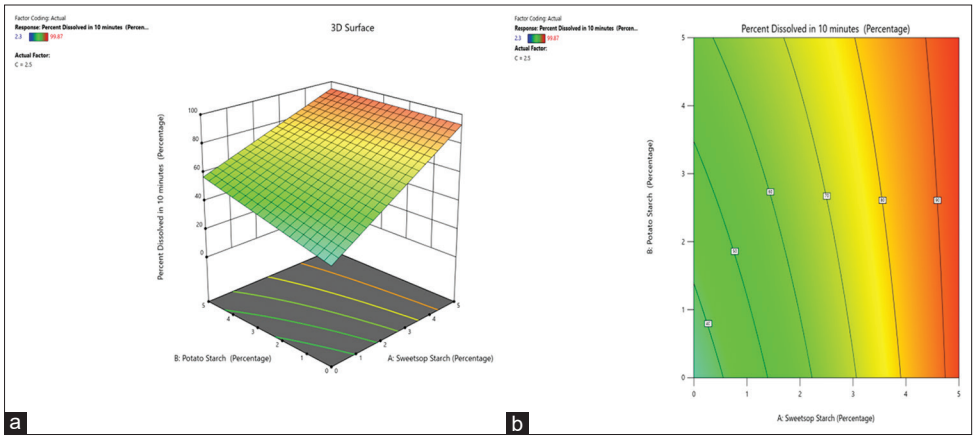

Fig. 16: (a) RSP, (b) contour plots of Telmisartan fast-dissolving tablets (effect of sweetsop starch and potato starch on the percent drug dissolved in 10 min)

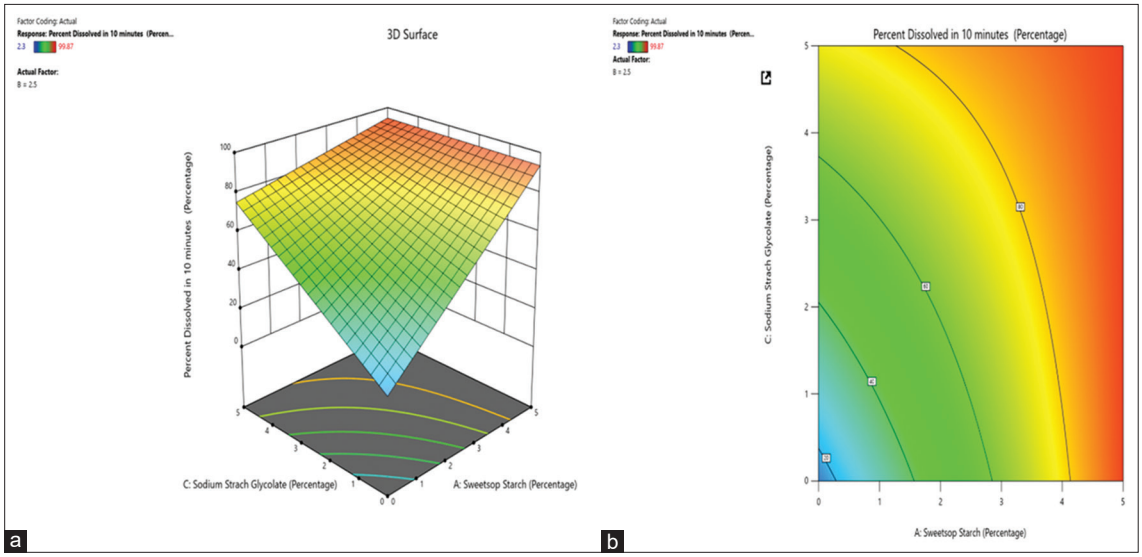

Fig. 17: (a) RSP, (b) contour plots of telmisartan fast-dissolving tablets (effect of sweetsop starch and sodium starch glycolate on the percent drug dissolved in 10 min)

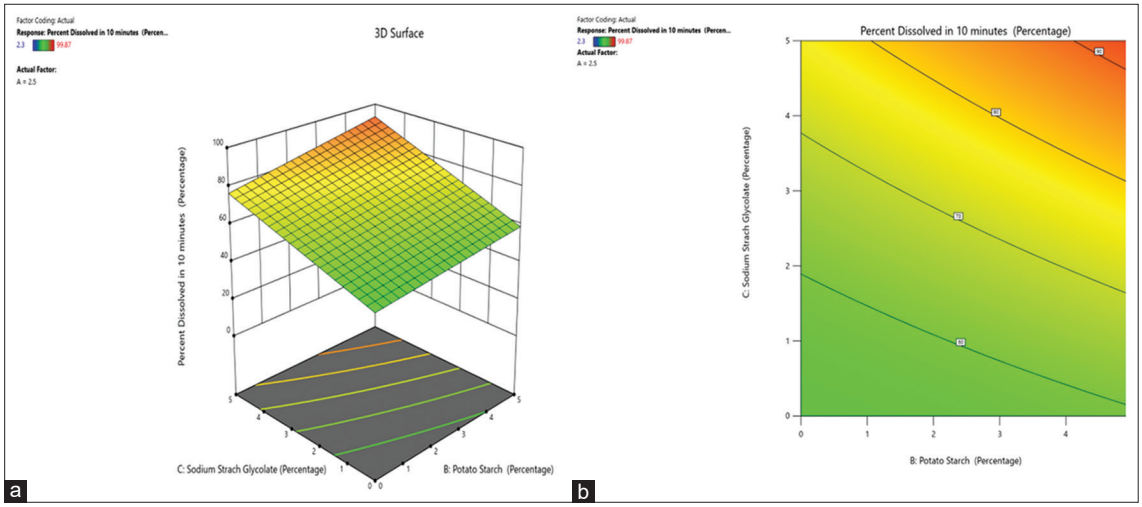

Fig. 18: (a) RSP, (b) contour plots of telmisartan fast-dissolving tablets (effect of potato starch and sodium starch glycolate on the percent drug dissolved in 10 min)

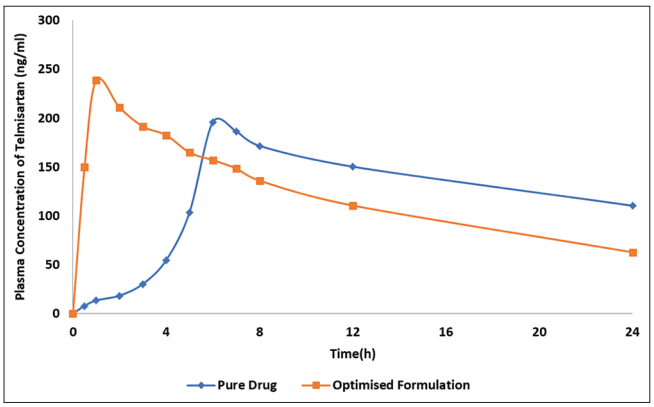

Fig. 19: *In vivo* pharmacokinetics of optimized formulation versus pure drug of TSN

Table 7: Pharmacokinetic parameters of TSN pure drug, optimized formula (TF2) with SSS

Parameter	Pure TSN (A)	Optimized TSN-FDTs formulation F2 employing SSS (B)
C_{max} (µg/mL)	197.74±0.20	238.74±0.25
T_{max} (h)	6.0	1.0
$AUC_{0-24\ h}$ (µg.h/ml)	2888.08±0.15	2971.42±0.20
$AUC_{0-\infty}$ (µg.h/ml)	5135.19±0.30	6693.20±0.40
BA (%)	-	76.5
K_a (h^{-1})	0.108±0.43	0.215±0.65
K_{el} (h^{-1})	0.029±0.25	0.049±0.25

SD: Standard deviation, SSS: Sweetsop starch, FDTs: Fast-dissolving tablets, AUC: Area under the curve, BA: Bioavailability, K_e: Rate of elimination, K_a: Rate of absorption constant. Data are given as mean±SD, n=6

Stability studies

For 6 months, the FDT formulations' physical characteristics, WT, water absorption ratio, DT, hardness, and *in vitro* drug release were observed. The results show non-significant differences ($p>0.05$) in the characteristics of before and after stability; the results are shown in Fig. 20 and Table 8.

Table 8: Summary of stability studies of optimized formulation

Formulation (F2)	Drug content (mg/tab) n±SD	Wetting time (Sec) n±SD	Water absorption ratio (%) n±SD	DT (sec) n±SD	*In vitro* drug dissolution (%)	Hardness (kg/cm^2) n±SD
Before stability	39.21±0.31	59±0.14	74±0.03	42±02	97.54±2.31	4.0±0.001
After stability	39.32±0.13	59±0.05	72±0.003	41±1.2	97.12±1.53	3.9±0.03

SD: Standard deviation, DT: Disintegration time, * n=6, mean±SD

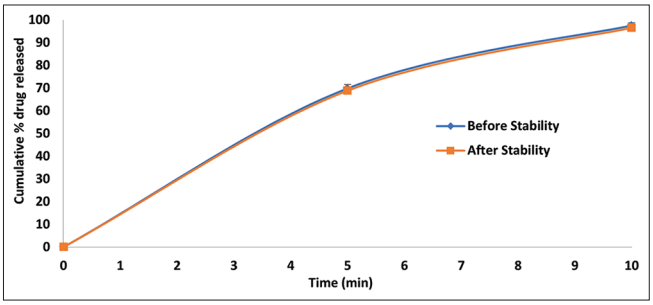

Fig. 20: *In vitro* dissolution profiles of optimized formulation during the stability study

CONCLUSION

The new superdisintegrant, SSS, had been extracted from the pulp of the sweetsop fruit. It was fine, crystalline, and free-flowing with superdisintegrant characteristics. SSG and SSS, as novel super disintegrants, were used to make carvedilol FDTs using a direct compression approach with a 2^3 factorial design. The optimal formulation of TSN (TF2) FDTs with 5% SSS had an acceptable DT, maximum dissolution, and enhanced relative BA without affecting the stability of the formulations. Hence, SSS was recommended to be utilized as a new natural superdisintegrant to enhance the *in vitro* dissolution and relative BA of selected poorly soluble drugs.

AUTHOR'S CONTRIBUTION

The authors report that this publication is based on the Ph.D. thesis (Chakradhar D), who conducted the preliminary research, collected the data, carried out the work, and produced the entire manuscript. Santosh Kumar R was the supervisor, and he revised the text and validated the data for this study.

CONFLICT OF INTEREST

All authors have none to declare.

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