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OCTENYL SUCCINATE CASSAVA STARCH AS AN EXCIPIENT FOR CONTROLLED RELEASE OF THEOPHYLLINE: MICROWAVE-ASSISTED SYNTHESIS, CHARACTERIZATION AND *IN-VITRO* DRUG RELEASE STUDIES

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ABSTRACT: Octenyl succinate derivatives (OSA) of cassava starch having different degree of substitution (DS) were synthesized by microwave irradiation in solid state using a monomode reactor and the drug, theophylline (Thp) was successfully incorporated in the modified starches for getting controlled release properties. The reaction conditions were optimized for maximizing the DS by response surface methodology and it ranged from 0.002 to 0.021, for the different modified starches. Pre-formulation study was done by Fourier transformed infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) for testing the drug-excipient compatibility. Drug incorporated tablets were prepared using the modified starches and their properties were studied. The spectral and DSC studies showed that there was a good compatibility between OSA starch matrix and theophylline. The *in vitro* drug release study was performed under different conditions of pH and time as well as after storage of the tablets for different time durations. The *in vitro* release rate was found to be significantly related to the DS of the modified starch and more sustained release of the drug was observed with the matrix incorporated with OSA starch of higher DS. Kinetics studies showed that the drug release obeyed Higuchi model and the release mechanism was coupled diffusion and erosion.

INTRODUCTION: In recent years, biomaterials have been introduced as controlled release tablet matrices due to their abundant availability, low cost, biodegradability and non-toxicity. In addition, many polysaccharides including starch can form non-covalent bonds with biological tissues forming bio-adhesion. These bio-adhesive polysaccharides can extend the residence time and therefore enhance the absorption of the incorporated drugs [1]. However, in such applications, starch has some limitations like hydrophilicity resulting in the fast release of incorporated drug in the foregut.

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This indicates the poor incorporation of drug in the native starch matrix and therefore, native starch is not suitable for the sustained release of drugs. Modification on starch back bone will make it an efficient matrix for pharmaceutical application [2].

Among the various commercial sources of starch, cassava (tapioca) deserves particular attention because of the purity and bland taste of its starch due to the lack of lipids, protein and other such compounds compared to starch from cereals, legumes and other roots and tubers like potato. Hence, modified forms of this starch can be a better matrix for pharmaceutical applications including drug delivery. Presently, the commercial exploitation of cassava starch is mainly limited to food, textile and adhesive industries. For introducing hydrophobicity to starch one of the methods used is esterification with octenyl succinic

anhydride (OSA), which introduces hydrophobicity on starch without altering its hydrophilicity [3]. Due to the resulting amphiphilic character, OSA starch can act as an effective emulsifier [4] and a sustained release matrix for various drugs [5].

Most of the earlier studies on starch esterification with OSA use conventional processes, where the reaction time for esterification was usually very long [6, 7]. This is due to the difficulty in the introduction of bulky octenyl groups into the starch backbone. Microwave technique has been reported as a fast and efficient method especially for the esterification reactions of starch in dry state [8]. The present investigation was aimed at optimizing the conditions for the octenyl succinylation of cassava starch by solid phase microwave reaction and evaluation of the modified starch as sustained release matrix for the drug, theophylline.

MATERIALS AND METHODS:

Materials: Cassava starch was extracted from the freshly harvested tubers of the variety H-165.Octenyl succinic anhydride and the enzyme Pancreatin were purchased from Sigma Aldrich (St. Louis, USA) and Theophylline (Thp) was procured from Himedia Laboratories (Mumbai, India).

METHODS:

Synthesis of octenyl succinate starch: The reaction conditions for the synthesis of OSA starch were optimized using a three factor Box-Behnken design [9], which consisted of fifteen treatments. The factors and their levels used were: weight of octenyl succinic anhydride (OSA - 1, 2 and 3% based on starch dry weight), microwave irradiation time (5, 7 and 9 min) and temperature (40, 60 and 80°C).

The microwave power used was 600W in all cases. Starch (50 g) was powdered using a mortar and pestle. Octenyl succinic anhydride (OSA) was added and thoroughly mixed with the starch.

The mixture was taken in the glass reaction vessel of a monomode microwave reactor (Rotosynth Rotative Solid phase Microwave reactor, Milestone Srl, Vies Fatebenefratelli, Italy) and subjected to irradiation with rotation at the desired temperature for the required time. After reaction, the sample was cooled to ambient temperature and then slurried in distilled water. The pH of the slurry was adjusted to 6.5 with 0.5N NaOH solution and then filtered. The precipitate was washed 3-4 times with 100ml portions of distilled water and finally with acetone. After filtration, the product was dried in an air oven at 55ºC overnight and then ground.

Characterization of OSA starch:

Degree of substitution: The degree of substitution (DS) of the OSA derivatives of starch was determined according to a titrimetric method [10]. A known weight of the starch sample was dissolved in dimethyl sulphoxide at 70°C with swirling of the flask and heating was continued for 10 min. After cooling, 3-4 drops of phenolphthalein was added to the starch solution and then titrated against a standard solution of sodium hydroxide (NaOH) till the appearance of pink colour. The DS was calculated using the following equation:

$$DS = (0.162 \times \frac{V \times M}{W}) / (1 - 0.210 \times \frac{V \times M}{W})$$

Where, V is the volume of NaOH (mL) used during titration, M is the molarity of NaOH and W is the weight of the starch sample.

Swelling power: A weighed quantity of the modified starch was incubated at 37°C for 2h in simulated gastric fluid (0.1M hydrochloric acid containing 0.32% w/v pepsin), followed by incubation for 6h in simulated intestinal fluid (0.2M phosphate buffer containing 1% w/w Pancreatin). The swelling ratio was calculated from the weights of the swollen starch and the dried starch after the treatment [3].

Scanning electron microscopy: The ultra structure of the gold coated starch samples was studied using a scanning electron microscope (JEOL/EO model JSM-6390, JEOL, Tokyo, Japan) operating at 15 KV.

X-ray diffraction analysis: The powder X-ray diffraction analysis of the modified starches was done using a Bruker X-ray diffractometer (Model D8 Advance, Bruker AXS Inc., Madison, W1 USA) with Cu Kα radiation (λ = 0.15406nm).

Pre-formulation study:

Differential scanning calorimetry: For determining the drug-excipient compatibility,

thermal analysis of theophylline as well as theophylline mixed with excipient and other ingredients of the tablet, were carried out using a differential scanning calorimeter (DSC 22e, Mettler Schcoerfenbach, Switzerland). Binary mixtures of theophylline and excipient (1:1 weight ratio) were prepared by the physical mixture technique [11]. The melting temperature (T_m) was determined by heating 5 mg of the sample in a sealed DSC pan from 30 to 300^{o}C at a rate of 20^{o}C/min and then cooling to 30^{o}C at the same rate. An empty pan was used as reference. The peak of the melting curve was taken as T_m and the corresponding enthalpy of melting was also recorded.

FTIR analysis: The infrared spectra of the OSA starch and the theophylline-starch mixtures were recorded on a Perkin Elmer FTIR instrument (Spectrum RX1, Perkin Elmer, Norwalk, CT, USA) using a diffused reflectance accessory (DRA) for powder samples. The spectrum of KBr was taken as the background.

Preparation of drug incorporated tablets: The tablets were prepared by wet granulation method. The OSA starch and theophylline were mixed thoroughly with gelatinized cassava starch (5% w/w) and dried at 100^{o}C for further tablet production.

Then, talc (1.67% w/w) and magnesium stearate (0.83%w/w) were added as lubricants and mixed for 5 minutes using a mortar and pestle. The tablet weight was fixed as 600 mg which contained 100 mg of theophylline along with other excipients. Six hundred milligram quantities of 500 – 1000 μm size fractions of the granules from each formulation were weighed and compressed by using a Cadmach Rotary tableting machine at a constant pressure of 8 Tons. The punches and dies used were flat faced with a die diameter of 13 mm.

Physical characterization of tablets: The tablets were characterized by determining their weight and thickness. To verify the uniformity of tablets from each formulation, 10 tablets were taken and weight was measured using an electronic balance. The mean weight was expressed in mg. The thickness and diameter of 10 tablets from each formulation was measured using Vernier Calipers and the mean values were expressed in mm.

Dynamic mechanical analysis of tablets: The dynamic moduli of the tablets were determined according to the procedure of Onofre et al.[12] with slight modifications. Theophylline loaded tablet was placed on a cover glass and 5mL of deionised water was added to it. It was then allowed to stand for 15 min for water penetration into the tablet. The swollen tablet was used for frequency sweep and creep tests.

Frequency sweep test: The swollen tablet was placed on the bottom plate of the US 200 rheometer (Anton Paar, Germany) maintained at 25^{o}C and 20 mm parallel plate was then lowered to a gap of 4mm. Equilibration after 30s, a frequency sweep was initiated with 1-100 Hz and 0.2% strain. From the frequency sweep test, storage modulus (G′), loss modulus (G″) and complex viscosity (η) were determined as a function of frequency.

Creep test: After completion of frequency sweep up to 100Hz creep test was done with the same tablet. For this, the stress applied to the tablet was 1.2 Pa for 3 min, measured the compliance J (t) and the stress was removed and the recovery of the material was measured for 3 min.

***In- vitro* drug release and kinetics:** The release of drug from the tablets were studied *in -vitro* at pH 2.1 and 7.4. Theophylline incorporated tablets was placed in 100 mL of the dissolution media maintained at 37°C and kept under constant stirring at 100 rpm. 10 mL each of the dissolution fluid was withdrawn at different time intervals to determine the amount of drug released into the medium.

To maintain the sink conditions, the volume withdrawn was replaced with an equal volume of the release medium. The withdrawn solution was filtered, suitably diluted and its UV absorption was determined at 275nm using a UV-visible spectrophotometer (T80$^+$ UV/VIS spectrometer, London EC IV 4 PY UK) [13]. The drug release data were fitted to zero-order, first-order and Higuchi models to study the kinetics of Thp release from the tablets. The mechanism of drug release was determined by fitting the initial 60% drug release data to Korsmeyer–Peppas model [14].

Storage stability of the controlled release tablets: The theophylline controlled release tablets were stored in polypropylene bottles and kept in a stability chamber maintained at 40±2ºC RH for six months [15]. The *in vitro* drug release from the tablets as well as the kinetics were determined at three months and six months after storage to study the storage stability.

Statistical analysis: Analysis of variance (ANOVA) was performed using the package SAS 9.3. Second order polynomial equations and surface plots were generated using significant parameters (p<0.05). Duncan Multiple Range Test (DMRT) was done for making pair-wise comparisons of the mean values. Pearson correlation analysis was performed to study the correlation between drug release and physical properties of the tablets.

RESULTS AND DISCUSSION:

Optimization of the synthesis of OSA starch: The degree of substitution of OSA starches synthesised by solid phase microwave reaction using response surface design of the variables selected, varied from 0.002 to 0.021 **(Table 1)**.

TABLE 1: DEGREE OF SUBSTITUTION (DS) AND SWELLING POWER OF OCTENYL SUCCINATE DERIVATIVES OF CASSAVA STARCH SYNTHESISED BY MICROWAVE TECHNIQUE

Sample	Weight of OSA (% based on starch dry wt.)	Time (minutes)	Temperature (ºC)	DS	Swelling power (SGF*)	Swelling power (SIF**)
S1	1	5	60	0.004±0.001	1.83±0.02	2.09±0.05
S2	1	9	60	0.007±0.002	2.19±0.07	2.23±0.03
S3	3	5	60	0.016±0.001	2.45±0.03	2.72±0.05
S4	3	9	60	0.021±0.001	2.74±0.01	2.91±0.02
S5	1	7	40	0.004±0.001	1.85±0.04	2.15±0.04
S6	1	7	80	0.002±0.001	1.74±0.06	2.16±0.05
S7	3	7	40	0.016±0.001	2.5±0.02	2.65±0.12
S8	3	7	80	0.006±0.002	2.08±0.01	2.26±0.03
S9	2	5	40	0.014±0.001	2.25±0.05	2.62±0.06
S10	2	5	80	0.005±0.002	2.03±0.04	2.15±0.02
S11	2	9	40	0.017±0.001	2.55±0.02	2.71±0.13
S12	2	9	80	0.005±0.002	1.96±0.03	2.14±0.01
S13	2	7	60	0.012±0.001	2.31±0.08	2.64±0.06
S14	2	7	60	0.013±0.001	2.28±0.01	2.61±0.02
S15	2	7	60	0.013±0.001	2.39±0.01	2.64±0.01
Native starch	-	-	-	-	1.64±0.06	2.01±0.03

*Simulated gastric fluid **Simulated intestinal fluid

According to the FDA regulations, octenyl succinate derivatives with a DS up to 0.02 are permitted as a food ingredient [16]. These derivatives can therefore be safely used in incorporation of drugs. Sample S4 synthesized under the following conditions showed the highest DS of 0.021: weight of octenyl succinic anhydride= 3 g/100 g of starch, microwave exposure time = 9 min and temperature = 60°C.

The weight of octenyl succinic anhydride (X_1) and temperature of the reaction medium(X_2) had significant effects on DS, and an increase in the levels of these parameters resulted in an increase in the DS of the modified starches. Both these parameters also showed a quadratic effect so that DS increased as the temperature or the weight of OSA increased up to a particular level and then decreased. The DS of the OSA starches had an adequate fit to a quadratic polynomial model (p<0.05) as represented by equation 1, in which only the significant effects were retained. The value of determination coefficient, R^2 illustrates the higher predictability of the proposed model for the reaction. The three dimensional response surfaces show the change in DS with respect to the weight of octenyl succinic anhydride and temperature **(Figure 1)**.

$$DS = -0.041 + 0.019X_1 + 0.001X_3 - 0.004X_1^2 - 0.00001X_3^2 (R^2 = 94\%)$$ **…… Equation 1**

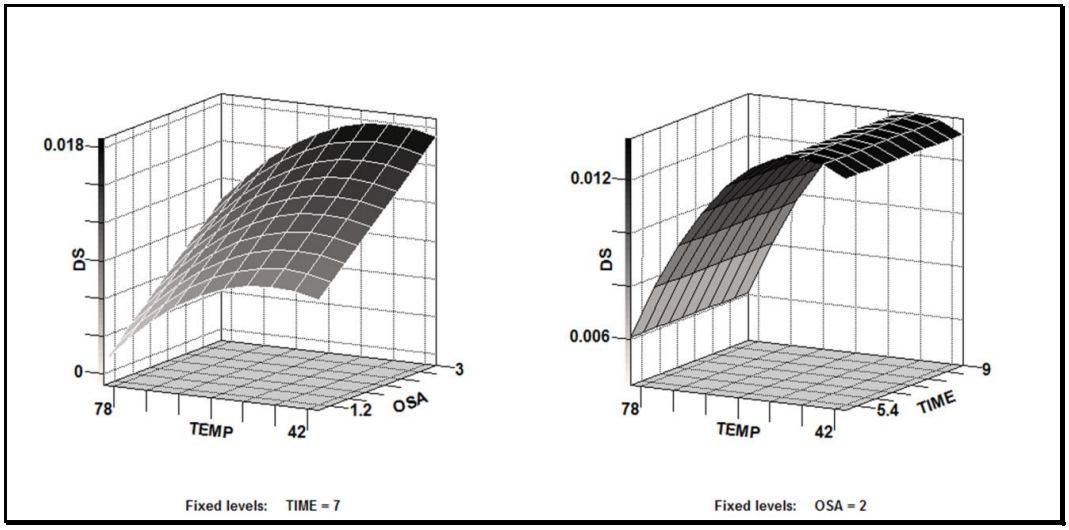
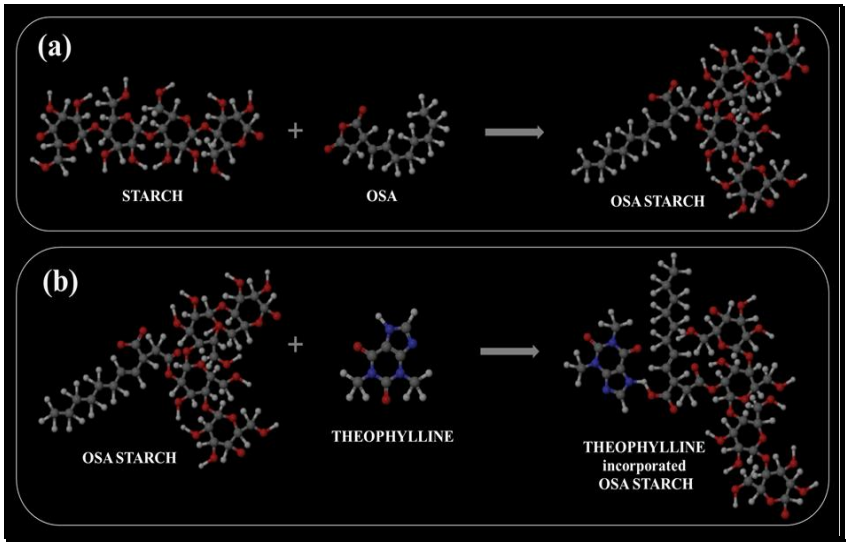


FIGURE 1: RESPONSE SURFACE PLOTS SHOWING THE EFFECT OF REACTION CONDITIONS ON THE DS OF OSA STARCH

Swelling power: Swelling power is an important index to decide the controlled release ability of the carrier material of the drugs. In the present study, the octenylsuccinate starch with higher DS exhibited more swelling power in simulated fluids than those with lower DS. The swelling power was found to be more in simulated intestinal fluid (SIF) (pH 7.4) than in simulated gastric fluid (SGF) (pH 2.1) **(Table 1)**. The highest swelling power (2.91g/g) was obtained for the sample with DS 0.02 at pH 7.4, whereas, it was 2.01g/g for the native cassava starch at the same pH. At pH 2.1, the highest swelling power (2.74g/g) was observed for OSA starch with DS 0.02, and for the native starch it was1.64g/g. Simple correlation analysis showed that DS is significantly (p<0.0001) correlated to the swelling power with a correlation coefficient of 0.95. Due to the presence of bulky OSA groups containing hydrophilic carboxyl groups in the modified starch, more water gets trapped into the polymer and therefore the swelling capacity of the polymer increases.

At higher DS, the number of carboxyl groups also increases resulting in increase in swelling power of the OSA starch. The weakening of intermolecular hydrogen bonding between starch molecules due to the introduction of bulky OSA groups also supplements to the increased water holding ability of OSA starch. This result is in agreement with the findings of Wang et al.[3] The mechanism of reaction between starch and octenyl succinic anhydride to form the OSA starch and the incorporation of theophylline in OSA starch matrix are represented in **Scheme 1**.



SCHEME 1: (A) MECHANISM OF OCTENYL SUCCINYLATION OF STARCH AND (B) INCORPORATION OF THEOPHYLLINE IN OSA STARCH

X-ray diffraction analysis: The X-ray diffraction analysis showed that the native as well as modified starches exhibited A- type crystalline pattern, which is typical of cassava starch with major reflection angles at16.8° (5.21), 17.95° (4.94) and 22.89° (3.88) **(Figure 2)**.

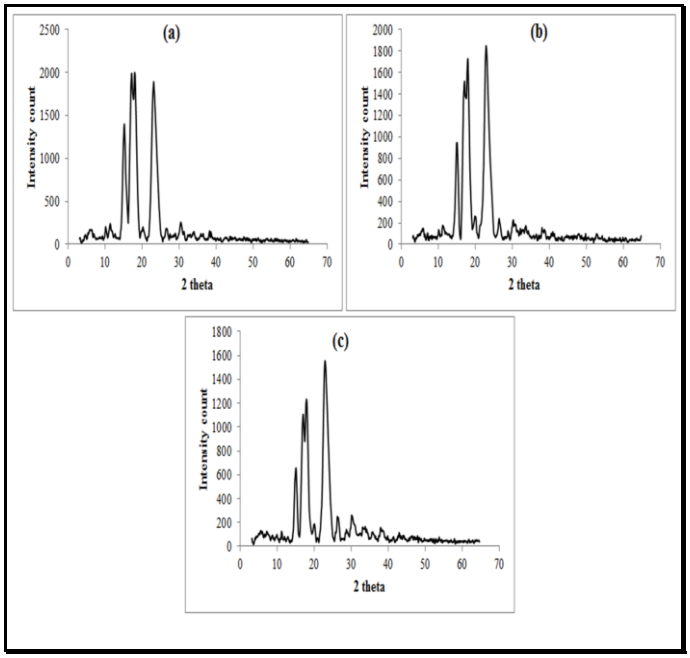


FIGURE 2: X-RAY DIFFRACTION PATTERNS OF (A) NATIVE STARCH (B) OSA STARCH WITH DS 0.016 AND (C) OSA STARCH WITH DS 0.02

This indicated that octenyl succinylation by microwave irradiation did not produce any change in the crystalline pattern [17]; however, lowering of peak intensity was observed. This could be due to the fact that modification of starch with octenyl succinic anhydride with low level of substitution mainly occurs in the amorphous region [18]. Chemical substitutions mainly occur in the amorphous domains of starch because amylose is located in the amorphous domains and is better accessible to esterification [16]. This result was in agreement with the findings of Song et al.[16].

Scanning electron microscopy: The esterification reaction of starch using microwave irradiation under the conditions used did not bring about any significant change in the granular features. The SEM images of the native cassava starch and starch octenyl succinate derivatives (with DS = 0.016 and 0.02) are shown in **Figure 3.**

The granular morphology of the modified starches was more or less similar to that of the native cassava starch. Most of the granules appeared in spherical or truncated shape with a hilum containing one or more pits at one end, which is the typical granular appearance of cassava starch. Therefore, modification of cassava starch by octenyl succinylation under microwave irradiation could produce derivatives without alteration in the granular nature and crystalline pattern, but with better swelling power.

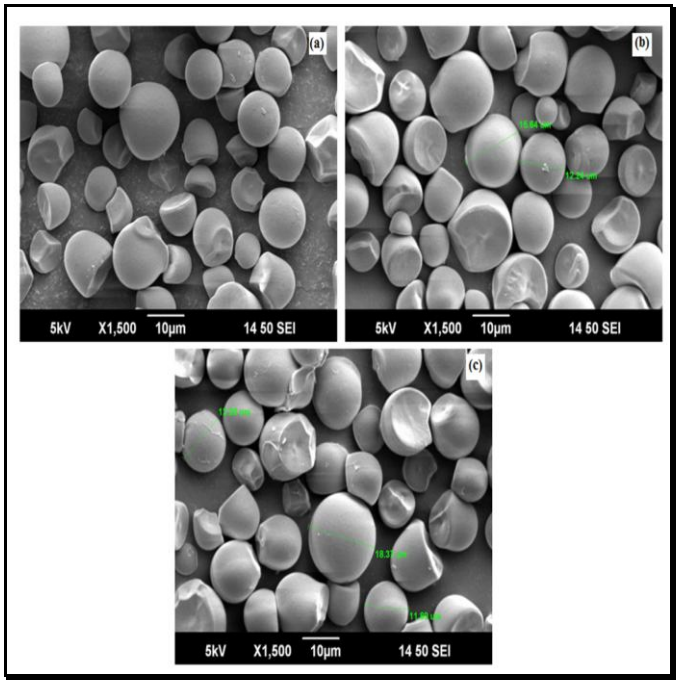


FIGURE 3: SCANNING ELECTRON MICROGRAPHS OF (a) NATIVE STARCH, (b OSA STARCH WITH DS 0.016 AND (c) OSA STARCH WITH DS 0.02

Pre-formulation study:

Differential scanning calorimetric analysis: DSC analysis was performed to find out the melting temperature and enthalpy of melting (ΔH) of theophylline and the theophylline-excipient mixtures. The melting temperature of the mixtures of Thp and OSA starch having different DS was found to be in the range of 270.3to 273.1°C, which was almost similar to that of Thp alone (272°C) **(Table 2)**.

This indicated that during the preparation of theophylline based tablets with different ingredients, theophylline retained its original nature in the tablets and no chemical change took place [11] suggesting that the OSA starch and the drug are Compatible with each other.

TABLE 2: MELTING TEMPERATURE AND ENTHALPY OF MELTING OF THEOPHYLLINE AND THEOPHYLLINE-EXCIPIENT MIXTURES

Sample	Melting temperature T_m (^oC)	ΔH (J/g)
Thp	272.0±1.0	30.1±0.9
Thp-S1	271.1±0.8	67.3±0.7
Thp-S2	272.3±0.9	88.1±1.1
Thp-S3	270.5±1.2	70.1±1.5
Thp-S 4	270.3±0.7	41.2±0.8
Thp-S5	271.5±0.5	49.3±0.3
Thp-S6	270.9±1.0	56.1±0.9
Thp-S7	271.3±1.3	91.16±1.1
Thp-S 8	271.5 ±0.9	35.1±0.6
Thp-S9	270.3±1.0	66.6±1.1
Thp-S10	273.1±0.1	85.5±1.0
Thp-S11	270.1±1.1	79.3±1.3
Thp-S12	270.3±0.8	68.5±0.9
Thp-S13	271.3±0.8	45.0±0.8
Thp-S14	270.5±1.0	76.8±1.1
Thp-S15	270.5±1.2	83.2±0.8
Thp-Magnesium stearate	270.5±1.0	51.8±1.0
Thp-Talc	270.3±1.2	80.3±1.2

*The drug: excipient ratio was 1:1 in all cases

FTIR analysis: The OSA starches exhibited all the characteristic absorption peaks of starch **(Figure 4)**. The absorptions in the fingerprint region corresponded to the C-O stretching vibration and the peak at about 2900cm^{-1} represents the C-H stretching vibration in starch. There was a broad peak at 3400cm^{-1}corresponding to the vibrational frequency of -OH groups in starch. In addition to the above peaks, in the IR spectrum of OSA starches, there was a peak around 1720cm^{-1} due to the carbonyl stretching vibration which confirms the introduction of carbonyl group corresponding to the ester in the starch backbone.

In the spectrum of Thp, the characteristic peak at 3457cm^{-1} corresponds to the stretching of imidazole –NH group. For the Thp loaded tablets, strong overlapping of peaks corresponding to the stretching of the amide group of Thp with the hydroxyl groups of OSA starch was observed at 3200-3340cm^{-1}. For Thp and Thp-excipient mixtures, the peak around 1709cm^{-1} represents the C=O stretching frequency.

The absorption of hydroxyl group of the drug loaded tablets was less intense and also slightly shifted to the lower frequency when compared to that of pure OSA starch. The shifting of hydroxyl band of Thp loaded tablets to lower frequency indicated an intermolecular hydrogen bonding between carbonyl group of Thp and hydroxyl group of OSA[13]. The Thp loaded tablets also showed all the characteristic peak of Thp, which revealed the chemical stability of Thp after incorporation into the OSA starch matrix.

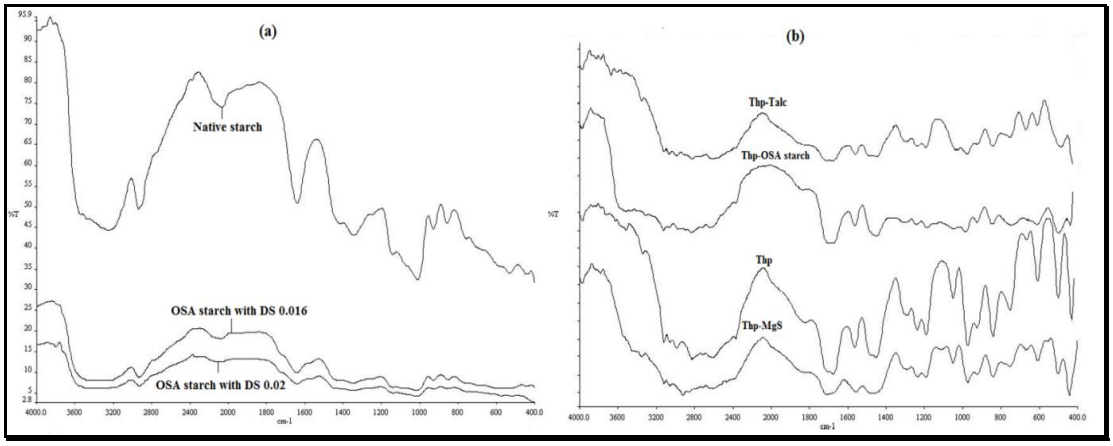


FIGURE 4: FTIR SPECTRA OF (a) NATIVE AND OSA STARCHES, AND (b) THEOPHYLLINE WITH VARIOUS INGREDIENTS IN THE TABLET

Physical characteristics of the tablets: The physical characteristics such as weight uniformity, thickness and diameter of the tablets, in which Thp was loaded on native starch as well as on OSA starches with varying DS, were measured and no significant differences were observed among the samples. The thickness and diameter of the all the tablets were in the range of 3.6±0.1 to 3.6±0.4 mm and 13.01±0.01 to 13.01±0.05respectively (data not shown). The weight uniformity of the tablets prepared from native as well as OSA starches were also similar and it was 600mg.

Dynamic mechanical analysis:

Frequency sweep: For all the samples, G′ was found to be greater than G″ implying the dominant elastic nature of these gel matrices. Both the

moduli were significantly higher for OSA starch based matrices (storage modulus 14600-26000Pa and loss modulus 6080-9420Pa) in comparison to that of native starch based tablets (4800-3210Pa) **(Table 3)**. The G′ values showed an increase at higher levels of modification and OSA starch with DS 0.02 (sample S4) had the highest G′ and G″. Therefore, S4 produced more rigid starch matrix and the release of drug occurs in a controlled manner. **Figure 5** shows the frequency dependence of the moduli. For all the samples, both G′ and G″ were independent of frequency at low frequencies, showing its more solid nature and 'true gel' characteristics, which is a favourable property of the drug release matrix [12, 19]. Systems that have strong frequency dependence are considered as 'weak gel' or viscous fluids [12, 20].

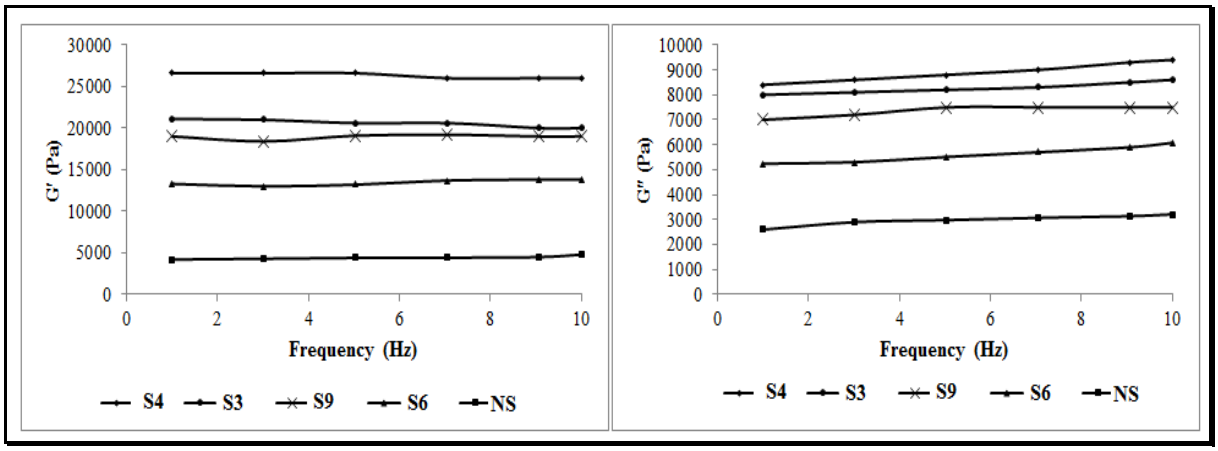


FIGURE 5: G' AND G" VALUES OF DIFFERENT TABLET FORMULATIONS AS A FUNCTION OF FREQUENCY

Onofre et al., (2010) also observed similar behaviour for cross-linked waxy corn starch based matrix. Compared to native starch, all the OSA starch based matrices showed higher G′ and G″ values at all frequencies suggesting that substitution with OSA groups led to progressive increase in gel like rigid structure. At higher frequencies G′ and G″ became higher for all the samples showing a steep increase (data not shown in figure), which could be due to the chain entanglements functioned as cross-links during oscillation [21]. The OSA starch matrices exhibited higher complex viscosity (142-483Pa.S) than that of native starch matrix (57.4 Pa.S) **(Table 3)** indicating the rigid nature of the former. An increase in substitution level led to an increase in viscosity of starch which is characteristic of less fluid rigid gel like systems.

TABLE 3: DYNAMIC MODULI, COMPLEX VISCOSITY (AT 10HZ) AND MAXIMUM CREEP COMPLIANCE OF OSA STARCHES AND NATIVE STARCH BASED TABLETS.

Sample	Storage modulus(Pa)	Loss modulus (Pa)	Complex viscosity (Pa.s)	Maximum creep compliance(1/Pa)
S1	14500±70.71	6310±28.3	200±6.3	0.0051±0.0004
S2	15300±141.4	6540±14.1	279±3.5	0.0034±0.0002
S3	20000±282.8	7550±35.3	295±4.2	0.0021±0.0004
S4	26000±212.1	9420±28.3	483±4.9	0.0021±0.0001
S5	14700±141.4	6310±7.07	197±3.5	0.0052±0.0004
S6	14600±212.1	6080±14.1	142±4.2	0.027±0.001
S7	22000±70.7	8530±14.1	328±6.3	0.0022±0.0002
S8	15000±282.8	6450±35.3	243±3.5	0.0043±0.0004
S9	20200±70.7	7530±21.2	300±7.0	0.0021±0.0001
S10	14900±353.5	6490±28.3	215±4.9	0.0051±0.0004
S11	23000±212.1	9010±14.1	412±6.3	0.0021±0.0002
S12	13800±70.7	6200±7.07	234±5.6	0.0042±0.0004
S13	18800±141.4	7080±14.1	220±3.4	0.0021±0.0004
S14	18700±424.4	7220±35.3	250±3.5	0.0021±0.0006
S15	19100±212.1	7400±14.1	279±3.4	0.0021±0.0004
NS	4800±70.7	3210±7.07	57.4±3.4	0.042±0.003

Creep test: The maximum creep compliance of various starch matrices calculated from the creep/recovery data is presented in **Table 3**. Creep test gives an idea about the molecular organization of carrier matrix, which helps to explain the drug release from the tablets [12]. The compliance of native starch matrix was the highest (0.042±0.0031/Pa).

The OSA starch matrices showed significantly lower creep compliance (0.0021- 0.0271/Pa) and this is in agreement with the frequency sweep data, in which OSA starch matrices showed higher values for the moduli. The decrease in compliance could be attributed to the formation of more rigid gel network [20], which is responsible for the more controlled release of theophylline from the OSA starch matrix, especially at the higher DS of 0.02.

***In vitro* drug release studies:** To understand the dissolution behaviour of theophylline from the OSA starch matrix, *in vitro* experiments were carried out at pH 2.1 and pH 7.4. The release of theophylline from the OSA starch matrix is due to the dissolution and diffusion of the drug when the tablets were placed in solutions having different pH. **Figure 6** illustrates a faster release of Thp from the native starch incorporated tablets compared to that from the tablets in which the drug was loaded on OSA starch.

It was also found that DS of the OSA starch had a significant effect on drug release from the tablets. The release was more sustained from the tablets incorporated with OSA starch of higher DS. As the DS of the starch increases, its swelling power also increases and consequently the incorporated drug takes more time to release into the medium. The drug release showed a dependence on the pH of the medium and at pH 7.4, the % release was more than at pH 2.1.

In the dissolution medium of pH 2.1, 100% of theophylline release occurred in 2h from the native starch incorporated tablets, while it was 8h in the case of tablets incorporated with OSA starch having a DS of 0.02 under the same conditions **(Figure 6a)**. At pH 7.4, it was completed after 6 h in the case of the OSA starch matrix (DS 0.02) **(Figure 6b)**.

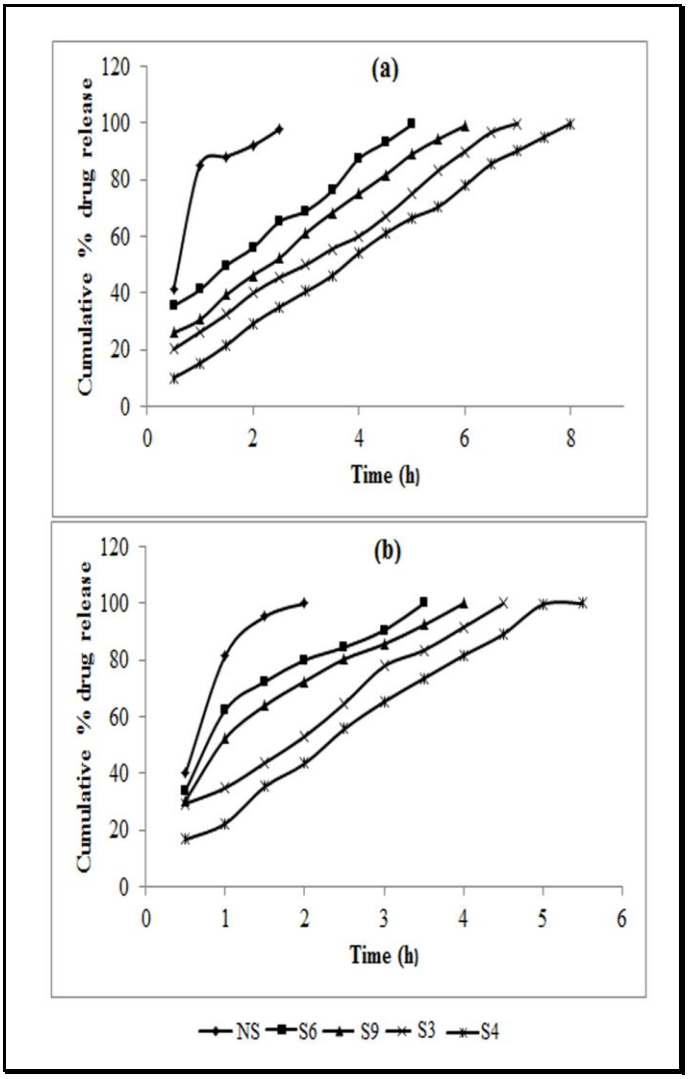


FIGURE 6: DRUG RELEASE PROFILE OF SUSTAINED RELEASE TABLET FORMULATIONS (a) AT pH 2.1 AND (b) AT pH 7.4

Kinetics of drug release: In order to study the kinetics of theophylline release from various starch based matrices, the release data were tested with different models which included zero order, first order and Higuchi model. For all the models, rate constant (K) and correlation coefficient (r^2) were calculated and the kinetics of Thp release was determined.

The r^2 and K values obtained in different models are presented in **Table 4**. From the r^2 values, it was found that the kinetics of drug release obeyed Higuchi model. The release mechanism of drugs from various matrices is different. The release may be only through diffusion or it may be only through erosion or sometimes both diffusion and erosion based upon the nature of the matrix in which the drug is incorporated. Korsemeyer-Peppas equation

gives an idea of mechanism of drug release from various matrices. In Korsemeyer-Peppas equation, 'n' represents the mechanism of drug release. When n=0.45, it represents Fikian diffusion and when n=0.89, it represents case II relaxational transport. When n values are in between 0.45 and 0.89, it represents non-Fickian transport which is related to both diffusion and erosion mechanisms [22]. In the present study, when the release data for the first 60% Thp release was fitted to Korsemeyer-Peppas equation, the 'n' values obtained were in between 0.45 and 0.89 **(Table 4)**. Therefore, the mechanism related to Thp release from various starch based matrices was non-Fikian diffusion. However, it was observed that the n values (0.708 - 0.718) were closer to that for case II relaxational transport for the matrices in which OSA starch, especially with higher DS, was incorporated.

TABLE 4: KINETIC PARAMETERS OF RELEASE OF THEOPHYLLINE FROM NATIVE AND OSA STARCH MATRICES IN DIFFERENT MODELS

Sample	Zero order		First order		Higuchi		Korsemeyer-Peppas model	
	r^2	K_0	r^2	K_1	r^2	K_H	r^2	n
Thp-NS	0.8524	23.54	0.9134	-0.49	0.9715	50.25	0.8854	0.58
Thp-S6	0.8962	20.10	0.9341	-0.45	0.9799	10.21	0.9625	0.613
Thp-S9	0.9525	7.54	0.9631	-0.41	0.9784	4.20	0.990	0.708
Thp-S3	0.9541	6.45	0.9658	-0.36	0.9741	4.31	0.993	0.716
Thp-S4	0.9654	8.09	0.9705	-0.20	0.9845	1.95	0.994	0.718

*NS represents native starch and S6, S9, S3 and S4 represent OSA starch with DS 0.002, 0.014, 0.016 and 0.02 respectively

Effect of storage on the drug release properties of the tablets: The percentage release of theophylline from the tablets at different pH was studied after 3 and 6 months of storage. The treatments NS, S3, S4, S6 and S9were evaluated after storage and the dissolution profile of fresh tablets before storage was taken as the reference. **Figure 7** shows the drug release pattern at pH 2.1 and 7.4 from the stored samples.

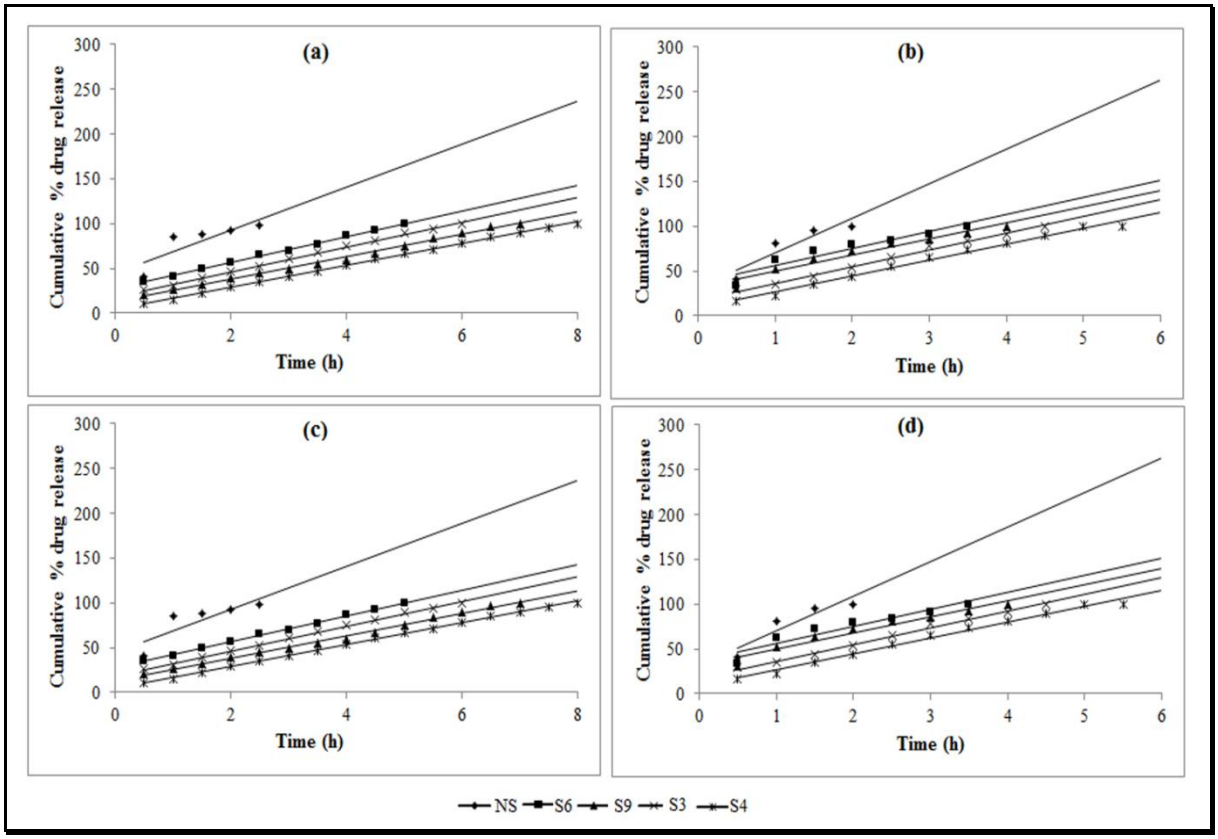


FIGURE 7: PERCENTAGE CUMULATIVE DRUG RELEASE FROM THE TABLETS AFTER STORAGE (a) & (b) 3 MONTHS AND (c) & (d) 6 MONTHS

The drug release profile was found to be similar for the reference sample and tablets stored for 3 and 6 months, at both the pH. The complete release of the drug from the OSA starch matrix occurred (DS=0.02) after 8 h at pH 2.1 and after 6 h at pH 7.4 for the stored samples also. Here also, the drug release rate was higher at pH 7.4 than that at pH 2.1 for all the samples. The study showed that the sustained release behaviour of theophylline from the OSA starch matrix was retained even after storage for several months. The release of drug from the tablets after storage also followed Higuchi model **(Table 5)**. The n values obtained from the Korsemeyer-Peppas model was found to be greater than 0.5 and therefore the drug release followed non-Fickian kinetics corresponding to diffusion and erosion similar to that of the reference sample. The study showed that the drug release pattern and kinetic model after storage of the drug up to 6 months was similar to that of the reference sample before storage and this shows the storage stability of the sustained release formulations.

TABLE 5: KINETIC PARAMETERS OF THEOPHYLLINE RELEASE FROM NATIVE ST AND OSA STARCH MATRICES AFTER STORAGE

After 3 months of storage								
Sample	**Zero order**		**First order**		**Higuchi**		**Korsemeyer-Peppas**	
	r^2	**K_0**	**r^2**	**K_1**	**r^2**	**K_H**	**r^2**	**n**
Thp-NS	0.8535	23.56	0.9142	-0.57	0.9713	50.21	0.8854	0.51
Thp-S6	0.8968	20.19	0.9348	-0.40	0.9797	10.29	0.967	0.610
Thp-S9	0.9531	7.59	0.9637	-0.49	0.9786	4.26	0.991	0.714
Thp-S3	0.9547	6.43	0.9664	-0.34	0.9745	4.37	0.994	0.701
Thp-S4	0.9659	8.11	0.9711	-0.26	0.9848	1.92	0.995	0.713
After 6 months of storage								
Thp-NS	0.8565	23.57	0.9178	-0.49	0.9725	50.35	0.8861	0.54
Thp-S6	0.8921	20.32	0.9349	-0.45	0.9791	10.46	0.9636	0.615
Thp-S9	0.9543	7.49	0.9647	-0.49	0.9780	4.47	0.994	0.710
Thp-S3	0.9511	6.47	0.9660	-0.38	0.9736	4.65	0.994	0.714
Thp-S4	0.9684	8.15	0.9785	-0.24	0.9858	2.01	0.987	0.719

*NS represents native starch and S6, S9, S3 and S4 represent OSA starch with DS 0.002, 0.014, 0.016 and 0.02 respectively

CONCLUSIONS: Octenyl succinate cassava starch was prepared by solid phase reaction by microwave irradiation which permitted to shorten the esterification time to less than 10 minutes in comparison to about 5-6h in the conventional method. The modified starches were tested as a controlled release matrix for the drug, theophylline by *in- vitro* methods. The swelling power of OSA starch in simulated gastric and intestinal fluids was higher than that of native starch and it increased with increase in DS.

The compatibility of the drug with OSA starch was studied by DSC and FTIR analyses. The *in -vitro* drug release rate was found to be in accordance with the DS of the OSA starch and more sustained release of drug was observed from OSA starch with higher DS. The drug release obeyed Higuchi kinetics and as per the 'n' value of Korsemeyer-Peppas model, the mechanism appeared to be coupled diffusion and erosion. The tablets also showed storage stability and the sustained release behaviour was retained even after storage for six months.

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