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Synthesis, Characterization and Evaluation of Modified Starches Derived from Tapioca Starch

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Over the past few decades, progressions in the preparation of starch-derived products from a variety of biodiverse sources have yielded substances with novel or improved characteristics. Present work focus on modification of tapioca starch by acids and anhydrides. Around 11 modified starches were synthesized using 9 acids and 2 anhydrides and characterized by FTIR spectroscopy and also their swelling property was also determined. For the optimization of molecular geometry, the HOMO and the LUMO modelling for initial starch and modified starch was performed by GAMES 64 software. Orbital investigations have revealed that the modified starch succinate form has an energy gap of 197 eV, indicating a loss in energy. This decrease in the energy of anhydride after reacting with starch shows the stability and absence of orbitals at the reaction site. Using modified starch, olmesartan tablets were formulated and compared with tablets prepared by crospovidone and croscarmellose sodium. In each instance, two distinct concentrations of the superdisintegrant (2% and 4%) were employed. Olmesartan tablets formulated dissolution rate adhered to first-order kinetics which was evidenced by R^2 values exceeding 0.940 across all the experiments. Notably, in the dissolution rate study, the modified starch exhibited rapid and enhanced dissolution of olmesartan from the tablets, comparable to the performance of commercial available super-disintegrants such as croscarmellose sodium and crospovidone.

Keywords: HOMO and LUMO modeling, Modified starch, Super disintegrant.

INTRODUCTION

Excipients as inert materials possess the ability to change the rate and degree of drug release, found to have an impact on the efficiency of system and pharmaceutical formulation. Natural excipients have been the focus of study in recent years, with the objective of substituting synthetic and chemical grade chemicals [1,2]. Among the vast varieties of excipients in oral dosage forms use of starch is extensive because it is an inexpensive, readily available biopolymer derived from plants such as rice, wheat, maize, potato, *etc*. Nonetheless, in its original state, its uses are restricted because of drawbacks including deterioration properties, lack of specific groups accountable for a given function and loss of viscosity and thickening power. Thus, alteration of starch is required to lessen its limits and enhance its applicability [3,4].

Modified starches find extensive application in the food sector as well as in the pharmaceutical, cosmetic, coating, oil exploiting fluid and other industries as additives. Starch modified from the natural starches obtained from different sources posses different properties [5]. The modification of starch obtained from tubers were exhibiting different disintegrating properties. The tapioca starch derived from South America cassava root serves as a dietary cornerstone in several regions across Africa, Asia and South America [6] was considered as it is lauded for its ease of cultivation. Despite its prevalence, tapioca offers minimal nutritional value due to its almost similar pure starch composition.

Modified tapioca starch, a vital food additive, undergoes a transformative process wherein starch or starch granules are subjected to treatments that result in partial degradation. This

alteration inspire it with properties essential for various applications, such as thickening, stabilizing or emulsifying in both food production and pharmaceuticals [7,8]. Simultaneously, the application range of chemical approaches for modification is also explored, especially with the help of newly developed chemical techniques, since they offer more choices for the transformation of starch than physical and genetic engineering alterations [9]. Starch typically reacts with tiny molecules to produce traditional chemical changes such esterification and etherification, cationization, oxidation and crosslinking. When starch is esterified, the reaction either happens at the outside surface of the starch molecule, maintaining the internal crystalline structure or it happens on the entire starch chains to generate traditional starch esters [10,11].

The modification entails exposing tapioca starch to agents like acids, enzymes or heat, which fundamentally reshape its molecular structure gluten-free alternative known as "Expandex" emerges from this modified tapioca starch [12]. Maize starch is the go-to binding ingredient for many Indian tablet and capsule manufacturers, however, still several crucial excipients are expensively imported from other countries [13].

Taking into consideration that tuber crops contain a variety of starches with different characteristics, this study aims to investigate the potential of different tuber starches and their derivatives as excipients for tablet and capsule formulations. Therefore, the current endeavor aims to modify tapioca starch using acids and anhydrides, assess its physical attributes, swelling behaviour and ultimately formulate its applications.

EXPERIMENTAL

Anaytical grade acids such as phosphotungstic acid, oxalic acid, citric acid, nicotinic acid, tartaric acid, benzoic acid, tannic acid and succinic anhydride, maleic anhydride, succinic anhydride were procured from S.D. Fine Chemicals, India. Tapioca tubers were sourced from local market in Vijayawada city, India.

Extraction: The tapioca tubers underwent a thorough cleaning process with distilled water, followed by peeling and an additional round of cleaning. Subsequently, the tubers were sliced into small pieces. Utilizing a local laboratory hammer mill, the fragments were finely ground into a paste and the resulting slurry underwent squeezing using a cheese cloth. The slurry obtained was kept aside and at intervals, the supernatant liquid was decanted. The starch slurry was then re-suspended in distilled water. After 72 h, cake of starch was recovered from the settled filter and then dried in a hot air oven at 50 ºC for 48 h. Bulk was pounded using a laboratory blender and further sieved through a 125 micron mesh sieve [14].

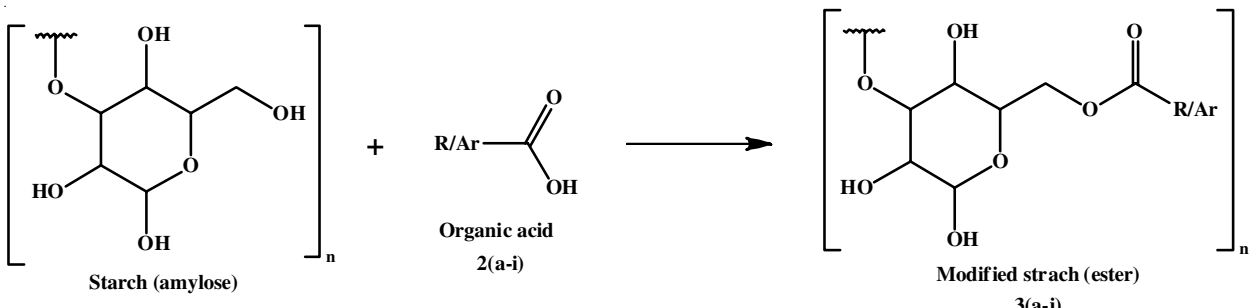
Preparation of modified starch: Extracted tapioca starch used for modification was analyzed qualitatively for the determination of various metabolites. Modified starches were prepared by with organic acids as well as with anhydrides [15].

Procedure with organic acids: A solution was prepared by dissolving 10 g of organic acid in 12.5 mL of water and this citric acid solution was combined with 10 g of starch powder. The pH of the resultant solution was adjusted to the range of 3.5-4 using 10 M NaOH solution. After the pH adjustment, the solution was transferred to a silicon tray and conditioned for 16 h at room temperature (28 ºC). Subsequently, the tray was placed in a hot-air oven and dried for 6 h at 60 ºC (**Scheme-I**). The resultant product was then pulverized, sieved through #80 and #40 sizes [16].

Procedure with anhydrides: In 10 g of starch powder, water was added until 90 g weight reached and allow the solution to mix swiftly followed by the pH adjustment of solution to 8.5-9.0 by adding NaOH (1 N) solution. Separately, weighed 20 g of acid anhydride was added to ethanol (10 mL) while stirring (magnetic stirrer) for 1 h and then mixed this solution with the previously prepared starch solution and adjust the pH to 6.5 with dil. HCl. Once the supernatant fluid has been separated and the suspension has been collected, transferrerd it to a silicon tray. A pressurized air oven was then used to dry the tray at 50 ºC for 48 h (**Scheme-II**). Following the drying process, the product underwent grinding and sieving through #80 and #40 sizes [17].

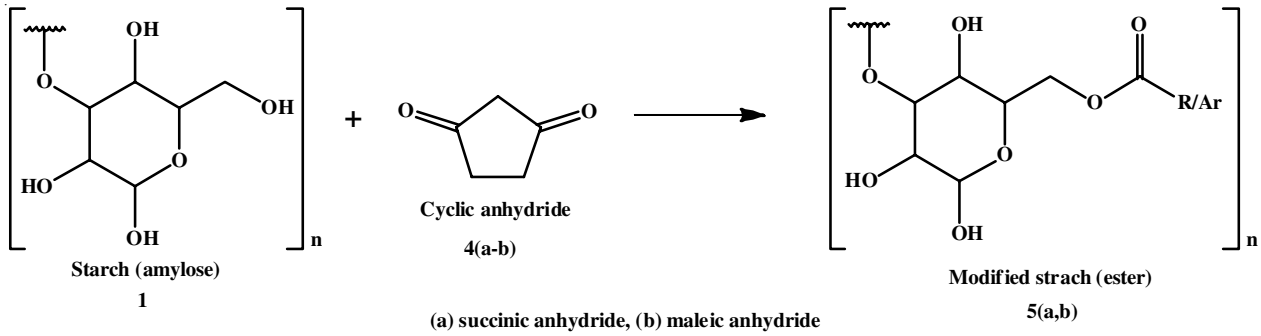
FTIR analysis: An FTIR-ATR spectrophotometer (Bruker Alpha II FTIR, Bruker Opus 8.1, India) was utilized to acquire the infrared spectra of neat and modified tapioca starches. The KBr pellet method was utilized at the scanning range of 4000 to 650 cm^{-1}.

Swelling index of modified starches: A starch sample (2 g) was placed in a pre-weighed 50 mL glass centrifuge tube and then the suspension was prepared by adding 10 mL of distilled water followed by heating at 55, 65, 75, 85 and 95 ºC for 40 min in a water bath with intermittent vortexing for every 2 min [18]. After cooling to room temperature, the suspension



(a) citric acid, (b) nicotinic acid, (c) tartaric acid, (d) phosphotungstic acid, (e) oxalic acid, (f) benzoic acid, (g) tannic acid, (h) succinic acid, (i) salicylic acid

Scheme-I: General scheme for the preparation of starch modification with acids



Scheme-II: General reaction for the preparation of starch modification with anhydrides

was centrifuged (2500 rpm for 15 min). Percentage gain in weight of the centrifuge tube represented the swelling power (SP). The supernatant was collected in pre-weighed moisture dishes and dried at 110 ºC for 12 h.

A 50 mL glass centrifuge tube was pre-weighed and filled with 2 g starch sample. After adding 10 mL of distilled water, the starch solution was heated at different temperatures of 55, 65, 75, 85 and 95 ºC for 30 min in a water bath with sporadic vortexing occurring every 2 min [19]. Following the room temperature cooling, the suspension underwent a centrifugation process (2500 rpm for 15 min). The swelling power (SP) was represented by the centrifuge tube's weight growth as a percentage. In moisture dishes that had been previously weighed, the supernatant was collected and dried for 12 h at 110 ºC.

$$SP\ (\%) = \frac{\text{Wt of sample tube after centrifugation}}{\text{Wt of tube with sample}} \times 100$$

Molecular orbital analysis of modified starches: In order to gain insights into the reactivity of starch and other reactants, the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) modeling using GAMES64 software were conducted. The MFF Gaussian method was employed to pinpoint specific orbitals within the molecular structure. Avagadro was used as graphic user interface for visualization of orbitals and energy determination [20].

Preparation of fast dissolving tablets of olmesartan by direct compression method: Fast dissolving tablets (FDTs) of olmesartan were prepared using dichloromethane (DCM), incorporating various super-disintegrants as outlined in the formulations provided in Table-1.

The specified amounts of olmesartan, lactose and polyvinylpyrrolidone (PVP), according to the formula for each case, were carefully mixed using a sealed polyethylene tube. Superdisintegrant, talc and magnesium stearate [$Mg(C_{18}H_{35}O_2)_2$] were then added and well mixed after being passed through a mesh no. #80 sieve.Then, the ingredient mixture was squeezed straight into tablets using an 8 station tablet punching machine equipped with a 9 mm die.

Disintegration: Using a disintegration tester (DBK Instrument, model 40 Tda 01, Mumbai, India), the time taken by tablets to dissolve in distilled water at 37 ± 0.5 ºC was measured.

RESULTS AND DISCUSSION

Tapioca starch was qualitatively analyzed in order to carry the presence of active constituents. The physico-chemical analysis confirmed the presence of carbohydrates, alkaloids such as colchicine, proteins, amino acids, triterpenoids and glycosides in the starch.

IR studies: From IR spectral data, it was observed that in pure starch peaks. The primary alcohol (-OH) stretching band is located at 1076 cm^{-1}, while the α-1,4-glycosidic linkage's vibration band is observed at 996 cm^{-1} and the characteristic groups of pure starch, including the intense hydroxyl group observed at 3400-3100 cm^{-1} and the ether linkage at 1140 cm^{-1}. In the modified starches the intensity of hydroxyl group decreased and conjugation peak at 1700-1650 cm^{-1} was observed, which confirmed the formation of ester linkage. The decreased intensity of the band ~3600 cm^{-1} is attributed to the O-H stretching, which implies that few O-H groups underwent carboxymethylation [21].

TABLE-1
FORMULAE OF OLMESARTAN TABLETS PREPARED BY DCM (DIRECT COMPRESSION METHOD)

Ingredients (mg/1 tablet)	Formulation					
	OD1	OD2	OD3	OD4	OD5	OD6
Olmesartan	40	40	40	40	40	40
Crospovidone	4.6	9.2	–	–	–	–
Starch Succinate	–	–	4.6	9.2	–	–
Croscarmellose sodium	–	–	–	–	4.6	9.2
Acacia	2.3	2.3	2.3	2.3	2.3	2.3
Talc	4.60	4.60	4.60	4.60	4.60	4.60
$Mg(C_{18}H_{35}O_2)_2$ (magnesium stearate)	4.60	4.60	4.60	4.60	4.60	4.60
Aerosil	2.3	2.3	2.3	2.3	2.3	2.3
Lactose	171.6	162.4	171.6	162.4	171.6	162.4
Total weight	230	230	230	230	230	230

Molecular orbital modeling: In HOMO and LUMO orbital modeling, it was observed that starch composed of amylose exhibits a zero energy gap. This suggests that the electron in the HOMO can readily move into the LUMO with the minimal energy requirement, indicating increased electron mobility. In case of succinic anhydride, the HOMO-LUMO difference was found to be +320 eV indicating its significant reactivity and stability [22]. After the reaction with succinic anhydride and starch the modified form shows an energy gap of 197 eV. This decrease in the energy of anhydride after reacting with starch shows the stability and absence of orbitals at the reaction site (Fig. 1). Selection of appropriate orbitals with lobes at the reaction sites is essential for accurate energy gap estimation. Additionally, the potential steric interactions should be carefully considered in the analysis. The energy gaps of the other molecules are tabulated in Table-2.

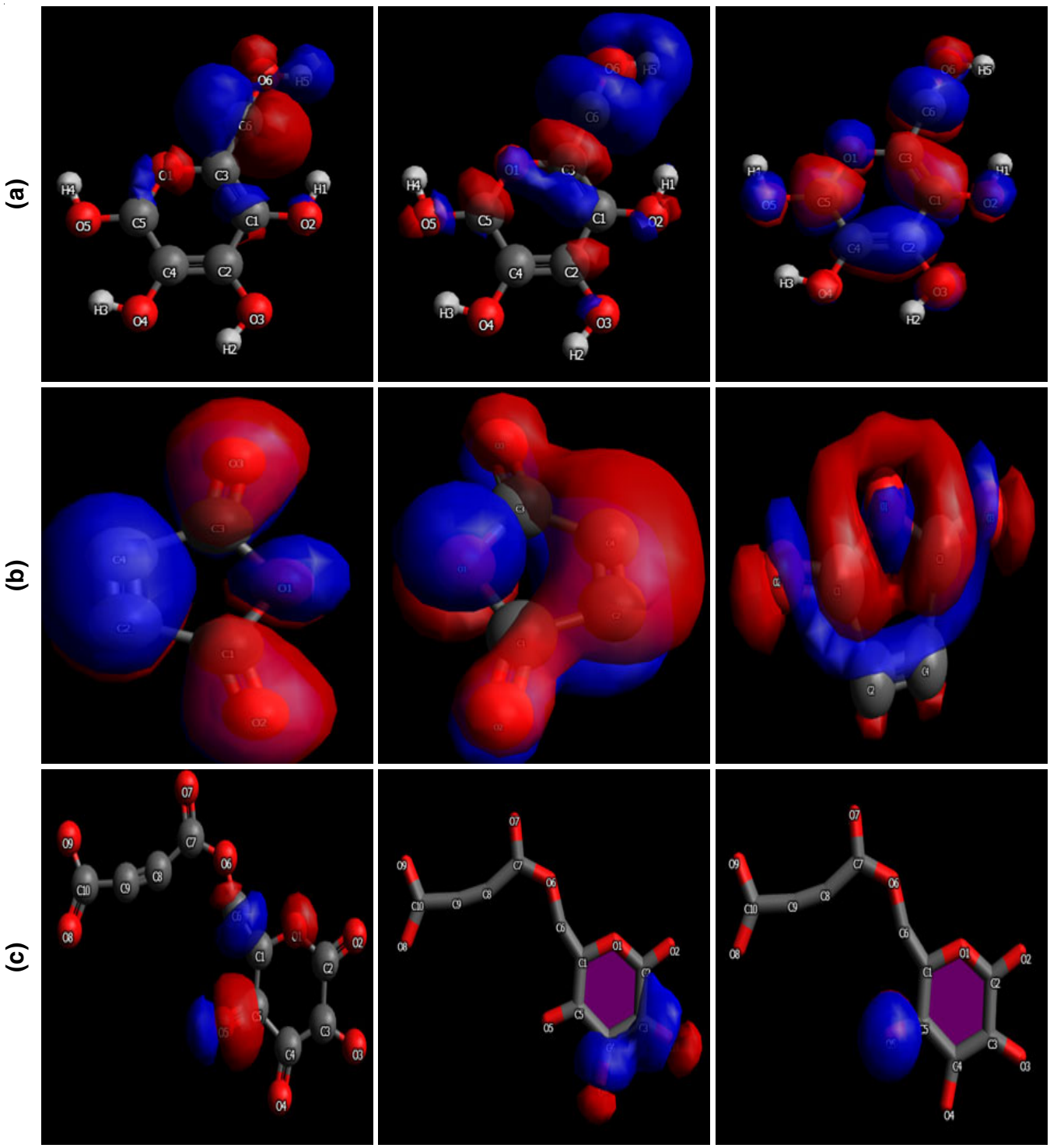


Fig. 1. HOMO-LUMO orbitals of (a) starch, energy: 105 kJ/mol, (b) succinic anhydride, energy: 210 kJ/mol and (c) starch succinate (modified starch), energy: 227 kJ/mol

TABLE-2
ENERGY GAP OF MOLECULAR ORBITALS

Reactant	LUMO	HOMO	Energy gap (eV)
Amylose	0	0	0
Succinic anhydride	68.193	-260.184	320
Modified starch	3649	3452	197

Swelling index: Swelling index of the modified starches is tabulated in Table-3, which indicate that the swelling property of succinic anhydride is very high when compared with other modifiers [23].

TABLE-3
THE SWELLING INDEX DATA OF MODIFIED STARCHES

Type of starch	Height (cm)
Starch citrate	0.2
Starch nicotinate	1.3
Starch tartarate	0
Starch phosphotungstate	0.5
Starch oxalate	0.4
Starch benzoate	0.4
Starch tannate	0.5
Starch succinate	0.4
Starch salicylate	0.3
Starch succinic anhydride	3.5
Starch maleic anhydride	1.2

Dissolution study rate on olmesartan FDTs: The dissolution rate of olmesartan tablets was investigated in 900 mL of phosphate buffer (pH 6.8) using an 8 station dissolution test apparatus LABINDIA, DISSO 8000 with paddle type stirrer of 50 rpm at 37 ºC ± 1 ºC. A single tablet formulation was utilized in each test. The dissolution fluid (5 mL) were taken at different times, filtered and then tested at 250 nm for olemesartan [24]. The withdrawn samples were substituted with new, drug-free dissolving fluid and corrections were made for the drug amount present in the withdrawn samples. Every experiment of dissolution was conducted in duplicate (n = 2). Dissolution profile of the tablets are shown in Fig. 2.

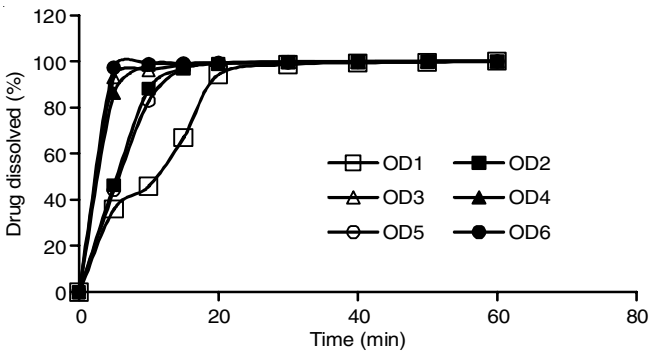


Fig. 2. Dissolution profiles of olmesartan; tablets prepared by direct compression method

Olmesartan tablets were formulated using three super disintegrants *e.g*. starch succinate, croscarmellose sodium and crospovidone. Two different concentrations of super disintegrant (2% and 4%) were employed in each case and the tablets were prepared using the direct compression method. The physical parameters, as presented in Table-4, showed the tablet hardness in the range of 3.0-4.5 kg/cm^2. The friability test indicated less than 0.75% weight loss in all cases. The drug content of the tablets met the criteria of 100 ± 3% of the labeled claim. All the tablets prepared disintegrated rapidly within 20 s. Among the three superdisintegrants, starch succinate also gave better disintegration results in comparison with crospovidone and croscarmellose sodium [20]. The rate of dissolution of olmesartan from the formulated tablets was examined in pH 6.8 phosphate buffer and all the olmesartan tablets exhibited rapid dissolution [25]. The dissolution kinetics followed first-order kinetics, with coefficient of determination (R^2) values exceeding 0.940 in all cases (Table-5).

TABLE-4
PHYSICAL PARAMETERS OF OLMESARTAN TABLETS PREPARED BY DCM (DIRECT COMPRESSION METHOD)

Formulation	Hardness (Kg/cm^2)	Friability (% wt loss)	Disintegration time (min-sec)	Drug content (%)
OD1	3.5	0.43	0-20	99.5 ± 0.25
OD2	3.7	0.29	0-18	100.20 ± 0.5
OD3	4.2	0.75	0-15	99.89 ± 0.65
OD4	3.8	0.45	0-12	98.99 ± 0.55
OD5	3.5	0.55	0-14	99.50 ± 0.65
OD6	3.2	0.28	0-11	99.35 ± 0.65

TABLE-5
DISSOLUTION PARAMETERS OF OLMESARTAN TABLETS PREPARED BY DCM (DIRECT COMPRESSION METHOD)

Formulation	PD_{10} (min)	DE_{30} (%)	Dissolution rate, K_1 (min^{-1})
OD1	45.90	30.28	0.1698
OD2	96.18	36.32	0.2777
OD3	82.74	31.83	0.2351
OD4	88.06	32.48	0.2388
OD5	98.44	31.83	0.2899
OD6	98.84	36.77	0.2984

Conclusion

In this work, among the modified starches synthesized from different acids and anhydrides, starch succinate demonstrated rapid and enhanced dissolution of olmesartan from the tablets, comparable to commercial super disintegrants such as croscarmellose sodium and crospovidone. Therefore, it can be concluded that starch succinate may serve as an alternative superdisintegrant in tablet formulations using the direct compression method.The reactive functional groups exposed during the amylose and amylopectin chains breakdown results in the swiftness of the reactivity of starch granules. Additional functional groups introduced through methods like chemical-oxidation, acetylation, phosphorylation with phosphoric acid, carboxymethylation and co-polymerization alter starch reactivity in water, oil, acids, enzymes and other chemicals. Moreover, crosslinking, formation of inter- and intramolecular bridges modifies starch reactivity and enhances its applicability in industrial and biological contexts.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. Q. Chen, H. Yu, L. Wang, Z. ul Abdin, Y. Chen, J. Wang, W. Zhou, X. Yang, R.U. Khan, H. Zhang and X. Chen, *RSC Adv.*, **5**, 67459 (2015); https://doi.org/10.1039/C5RA10849G
2. M. Haroon, L. Wang, H. Yu, N.M. Abbasi, Z.-A. Zain-ul-Abdin, M. Saleem, R.U. Khan, R.S. Ullah, Q. Chen and J. Wu, *RSC Adv.*, **6**, 78264 (2016); https://doi.org/10.1039/C6RA16795K
3. M.A. Otache, R.U. Duru, O. Achugasim and O.J. Abayeh, *J. Polym. Environ.*, **29**, 1379 (2021); https://doi.org/10.1007/s10924-020-02006-0
4. Y. Fan and F. Picchioni, *Carbohydr. Polym.*, **241**, 116350 (2020); https://doi.org/10.1016/j.carbpol.2020.116350
5. J. Compart, A. Singh, J. Fettke and A. Apriyanto, *Polymers*, **15**, 3491 (2023); https://doi.org/10.3390/polym15163491
6. M.Y. Naz, S.A. Sulaiman, B. Ariwahjoedi and K.Z. Shaari, *Scientific World J.*, **14**, 375206 (2014); https://doi.org/10.1155/2014/375206
7. E. Ojogbo, E.O. Ogunsona, T.H. Mekonnen, *Mater. Today Sustain*., **7-8**, 100028 (2020); https://doi.org/10.1016/j.mtsust.2019.100028
8. S. Suri and A. Singh, *Sustain. Food Technol.*, **1**, 348 (2023); https://doi.org/10.1039/D2FB00043A
9. Y. Fu, E. Jiang and Y. Yao, *Annu. Rev. Food Sci. Technol.*, **25** , 117 (2022); https://doi.org/10.1146/annurev-food-102821-035457
10. N. Masina, Y.E. Choonara, P. Kumar, L.C. du Toit, M. Govender, S. Indermun and V. Pillay, *Carbohydr. Polym.*, **157**, 1236 (2017); https://doi.org/10.1016/j.carbpol.2016.09.094
11. H. Nawaz, R. Waheed, M. Nawaz and D. Shahwar, Physical and Chemical Modifications in Starch Structure and Reactivity, In: Chemical Properties of Starch, IntechOpen, vol. 9, pp. 13-34 (2020).
12. R.S. Ayu, A. Khalina, A.S. Harmaen, K. Zaman, M. Jawaid and C.H. Lee, *Polymers*, **10**, 1187 (2018); https://doi.org/10.3390/polym10111187
13. M. Emeje and A. Rodrigues, in eds.: B. Valdez, Starch: From Food to Medicine, Scientific, Health and Social Aspects of the Food Industry, vol. 20, pp. 355-380 (2012).
14. M.-G. Dorantes-Fuertes, M.C. López-Méndez, G. Martínez-Castellanos, R.Á. Meléndez-Armenta and H.-E. Jiménez-Martínez, *Agronomy*, **14**, 865 (2024); https://doi.org/10.3390/agronomy14040865
15. S.M. Amaraweera, C. Gunathilake, O.H. Gunawardene, N.M. Fernando, D.B. Wanninayaka, R.S. Dassanayake, S.M. Rajapaksha, A. Manamperi, C.A.N. Fernando, A.K. Kulatunga and A. Manipura, *Molecules*, **26**, 6880 (2021); https://doi.org/10.3390/molecules26226880
16. N. Javadian, A. Mohammadi Nafchi and M. Bolandi, *Food Sci. Nutr.*, **9**, 5467 (2021); https://doi.org/10.1002/fsn3.2506
17. Y. Xu, Q. Chu, D. Chen and A. Fuentes, *Frontiers Mechanical Eng.*, **7**, 744001 (2021); https://doi.org/10.3389/fmech.2021.744001
18. O.A. Adetunji and O. Kolawole, *Nigerian J. Pharm. Res.*, **14**, 15 (2018).
19. H. Nawaz, M.A. Shad, S. Saleem, M.U. Khan, U. Nishan, T. Rasheed, M. Bilal and H.M. Iqbal, *Int. J. Biol. Macromol.*, **113**, 219 (2018); https://doi.org/10.1016/j.ijbiomac.2018.02.125
20. L. David, A. Thakkar, R. Mercado and O. Engkvist, *J. Cheminform.*, **12**, 56 (2020); https://doi.org/10.1186/s13321-020-00460-5
21. A. Okunlola, *East Cent. Afr. J. Pharm. Sci.*, **23**, 104 (2020).
22. V. Vamadevan and E. Bertoft, *Food Hydrocoll.*, **103**, 105663 (2020); https://doi.org/10.1016/j.foodhyd.2020.105663
23. C. Pozo, S. Rodríguez-Llamazares, R. Bouza, L. Barral, J. Castano, N. Müller and I. Restrepo, *J. Polym. Res.*, **25**, 266 (2018); https://doi.org/10.1007/s10965-018-1651-y
24. L. Lachman, A. Lieberman and J.L. Kinig, The Theory and Practice of Industrial Pharmacy,Varghese Publishing House, Delhi, India, pp. 67-68 (1991).
25. S.K. Battu, M.A. Repka, S. Majumdar and M. Rao, *Drug Dev. Ind. Pharm.*, **33**, 1225 (2007); https://doi.org/10.1080/03639040701377888