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Research Article

Compression and Release Properties of Two-Step Modified Rice Starch and Lactose Blends in Paracetamol Tablet Formulations

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ABSTRACT

Starches have been physically and/or chemically modified to improve their functional capacities, subsequently enhancing their use as excipients. Rice starch (*Oryza sativa* L. Family: Poaceae), was exposed to two-step modification and co-blended with lactose. The blends were incorporated in paracetamol formulations and evaluated for compression and release properties. Rice starch was simultaneously pregelatinized and silicified before co-blending with lactose at different ratios to obtain DMRS/L1:1, DMRS/L1:2, DMRS/L2:1. Similar blends containing unmodified rice starch and lactose (URS/L1:1, URS/L1:2, URS/L2:1) were also made. Density measurements, compressibility, surface morphology, particle size and FTIR spectroscopy were the assessment criteria for the blends, which were incorporated in paracetamol tablet formulations and evaluated for their release properties. Results were statistically evaluated using ANOVA at a significance level of p-values<0.05. Density measurements revealed higher angles of repose for the denser unmodified blends, indicating an enhancement of flow properties. DMRS/L1:2 and DMRS/L2:1 had good compressibility based on the Carr's indices of 24.17±0.02% and 21.78±0.16% respectively. Generally, the modified powder blends were more spherical, however DMRS/L2:1 had the largest particle size (39.58±2.37µm), while URS/L1:1 had the smallest particle size (11.50±1.31µm). Modification incorporated more functional groups without compromising the basic starch integrity as observed in the FTIR plots. Tablets containing modified starches disintegrated and released the API faster, with the formulation containing DMRS/L1:2 showing the fastest release rate. Dual modification involving simultaneous pregelatinization and silicification of rice starch led to enhanced functional properties when blended with lactose and showed better tablet qualities when incorporated as excipients.

Keywords: *Rice Starch; dual modification; physicochemical properties, lactose blends*

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INTRODUCTION

Starches are polysaccharides that can be obtained from different plant parts such as seeds, roots and tubers (Izuagie *et al.*, 2012). The usefulness of starches as excipients in drug formulations cannot be overemphasized. Excipients play exceptional roles of ensuring that the reproducibility in the pharmacologic activities of the Active Pharmaceutical Ingredient (API) is assured. Therefore, excipients are involved in both the manufacturing process and the therapeutic process (Apeji *et al*, 2013). Starches have been incorporated in dosage forms as binders (Musa *et al*, 2010), disintegrants (Adetunji *et al*, 2018) and fillers (Nishath *et al*, 2011), however, due to certain limitations of native starch, exemplified by low shear resistance, thermal resistance, increased probability for retrogradation, brittleness and decomposition, formulation scientists have researched into various methods of modifying starches, all in attempts to enhance the functional properties of starches and consequently improve on the final product that will be administered to the patient. Modifications to improve the versatility of starch can be categorized as physical or chemical, and the method adopted depends on the physicochemical properties of the native starch to be modified. Modified starches are seen as more superior because they possess enhanced characteristics such as increased flow, disintegration and ease of direct compression (in solid dosage forms). Physical modification involves the use of either heat,

moisture, granulation, gelatinization, extrusion or spray drying, while chemical modification involves the introduction of functional groups such as esterification, cationization, cross-linking, or hydrolysis and oxidation. (Hong *et al*., 2018). Pregelatinization is a form of physical modification of starch which involves heating and mechanical shearing, that leads to starch products that have improved water solubility and gelling properties (Hong *et al*., 2018). Addition of silicon dioxide to starches involves co-processing, mixing and heating colloidal silica with starch. Manju *et al* (2012) documented the improved disintegrant, flow and compression properties after native starch was modified with colloidal starch. Rice starch is a natural carbohydrate and a major component of rice, which is consumed globally as food. In its native form, the starch (obtained from *Oryza sativa* L. Family: *Poaceae*) is an insoluble white powder with fine granules, neutral taste, and clear white colour. In a previous work by Adetunji and Iorkua (2020) rice starch was modified by silicification and co-processed with starch obtained from *Dioscorea dumetorum*. Results obtained show that the flow properties of *Dioscorea dumetorum* starch were enhanced by conjugating it with silicified *Oryza sativa* starch. In the current study, rice starch was dually modified by both pregelatinization and silicification and the dually modified starch was characterized and incorporated as a disintegrant in paracetamol tablet formulations, in comparison with the native starch.

MATERIALS AND METHODS

Materials: The materials used include paracetamol BP powder (Shangqui Kangmeida Biotechnology Co. Ltd., China), corn starch BP (Lot 69833; from Bentos Pharmaceutical Products , Ibadan, Oyo State), lactose BP (Mitushi BioPharma Ltd, Ahmedalad, India), magnesium stearate powder (Fooding Group Limited, Shanxi, China), analytical grade silicon dioxide (Lobachemie laboratories , China), rice (*Oryza sativa*, Family: *Poaceae*) was purchased from a local market in Ibadan, South Western Nigeria, and authenticated (FHI No: 208671) at the Forest Herbarium, Ibadan, Nigeria. Distilled water was obtained from the Research Laboratory, Pharmaceutics and Industrial Pharmacy, University of Ibadan, Nigeria. All the other reagents used were of analytical grade and their use were modified as described.

Methods:

Extraction of Rice Starch: The rice grains were washed with distilled water and soaked for 48 h. The mixture was decanted, and the residue was washed again with distilled water and wet milled before sieving with muslin cloth. The filtrate was left standing for 12h before decanting. The entire process was repeated twice every 24 h daily for a further 96 h until all the starch was extracted. The residue was granulated by forcing through a 0.25mm mesh size sieve, and the granules were dried at 45 ^{0}C for 48 h, before storing the granules in air-tight containers.

Pregelatinization of Rice Starch: Exactly 150 g of rice starch was dissolved in 500 mL of water; the mixture was placed on a hot water bath (100^{0}C) and stirred continuously until a thick viscous product was obtained, which was spread on a tile and air dried before it was blended to powder form using Panasonic MX-AC 400. The pregelatinized powder was moistened and passed through a 0.25mm mesh size sieve to yield granules of pregelatinized rice starch, which was dried in the oven at 40 ^{o}C , before storing the granules of the dried pregelatinized rice starch in air-tight containers.

Silicification of Pregelatinized Rice Starch: Exactly 75g of pregelatinized starch was weighed and suspended using 187.5 mL of distilled water in a 500 mL beaker. Exactly 1.6g of colloidal silica was weighed and dispersed into the starch slurry with constant stirring for 5 minutes. The mixture was transferred to a water bath and heated with constant stirring for another 15 minutes, cooled before 150 mL of ethanol was added with continuous stirring. The precipitate was separated from the mixture and spread on a tray prior to drying in the oven at 40 ^{o}C. The flakes obtained were moistened with distilled water, forced through a sieve (0.25mm mesh size). The granules of the dual modified rice starch obtained were dried in the oven at 40 ^{o}C for 24 h. (Adetunji *et al*., 2018)

Preparation of Blends: Different granule blends containing different ratios (1:1, 1:2, and 2:1) of granules of the dual modified rice starch (DMRS) and lactose (L) were homogenously, but gently mixed in a mortar and pestle to obtain DMRS/$L_{1:1,}$ DMRS/$L_{1:2}$ and DMRS/$L_{2:1}$ respectively. Similar blends containing granules of unmodified rice starch (URS) and lactose (L) were also prepared to obtain URS/$L_{1:1}$, URS/$L_{1:2,}$ and URS/$L_{2:1}$ respectively.

Characterization of Blends

The six blends (DMRS/$L_{1:1,}$ DMRS/$L_{1:2}$, DMRS/$L_{2:1}$, URS/$L_{1:1}$, URS/$L_{1:2,}$ and URS/$L_{2:1}$) were characterized using the following parameters

Particle Size and Morphology: A light microscope with the aid of a calibrated eye piece was used to determine the particle sizes of the different blends. Surface morphology of the blends was determined using a desktop scanning electron microscope (FEI-XL 30SEM, Phenom World, Netherlands)

Bulk Density: Bulk densities (gcm^{-3}) were determined for the blends by pouring 30 gm of each sample into a 100 mL calibrated cylinder through a funnel. The height at which the powder reached was measured and the volume. The bulk density was calculated as the ratio of the mass of the sample to the volume of the sample in the cylinder as shown in Eq. (1). This was carried out in triplicates.

$$\text{Bulk density} = \frac{\text{Mass (gm)}}{\text{Volume (mL)}}\ \text{gcm}^{-3} \quad (1)$$

Tapped Density: Tapped densities (gcm^{-3}) were determined for the blends by pouring 30 gm of each sample into a 100 mL calibrated cylinder through a funnel and tapped for 3 min at 2 seconds intervals. The final volume at the end of the period was determined and the tapped density was calculated according to Eq. (2). This was carried out in triplicates.

$$\text{Tapped density} = \frac{\text{Mass (gm)}}{\text{Tapped Volume (mL)}}\ \text{gcm}^{-3} \quad (2)$$

Hausner's Ratio and Carr's Index: The values for the Hausner's ratio and Carr's index were obtained from the values of the bulk and tapped densities according to Eq. (3) and Eq. (4) respectively.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad (3)$$

$$\text{Carr's Index} = 100\left(\frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped Density}}\right) \quad (4)$$

Angle of Repose: Angle of repose was determined using an open cylinder of fixed diameter which was placed on a base (Fixed Height Cone method). Exactly 5g of each blend and starch were separately measured and allowed to flow freely through the orifice of the funnel to form a heap whose height and diameter were determined. The determination was done in triplicate. The angle of repose was calculated using the equation below:

$$\text{Tan}\,\Theta = \frac{h}{r} \quad (5)$$

Where h= height of powder, r = radius of circular heap

Fourier Transform Infrared (FTIR) Spectroscopy: A predetermined amount of each blend was mixed with potassium bromide and compressed into a thin disc using a hydraulic press. The potassium bromide disc was placed on the sample holder of a FTIR spectrometer (Magna IR 560 spectrophotometer-Perkin Elma, USA) and scanned at an infrared range of 4000 to 400 cm^{-1}. Spectra was obtained for each sample and the software was used to identify the peaks, functional groups and chemical bonds present in each sample

Compression and Evaluation of Tablets: Formulations containing 40 %w/w of paracetamol (500 mg), 59 %w/w of the granule blends and 1 %w/w magnesium stearate were directly compressed with a Carver Hydraulic press set at 0.75 metric tonne for 60 secs. Sufficient number of tablets were formulated per batch. Each set of tablets was stored under silica gel for a period of 24 h for elastic recovery to take place. After 24 h, the tablets were evaluated in triplicates for weight variation, uniformity of drug content, resistance to attrition, fracture resistance, disintegration and dissolution.

RESULTS AND DISCUSSION

Photomicrographs showing the morphology of the granules are shown in Fig.1, while Table 1 shows the physical properties of the six blends (DMRS/$L_{1:1}$, DMRS/$L_{1:2}$, DMRS/$L_{2:1}$, URS/$L_{1:1}$, URS/$L_{1:2}$, and URS/$L_{2:1}$). Generally, the unmodified rice starch (URS) blends were observed to be spherical, but appeared in clusters, while the pregelatinized rice starch (PRS) were more angular in shape, but with good spatial arrangement. The dual modified rice starch (DMRS) were observed to have more discrete particles with spherical shapes similar to those of the pregelatinized starch. Levels of particle-particle interaction could be a major determining factor to the flow of materials (Manju *et al.*, 2012). Particle shape has been indicated as a major factor that contributes to the ability of materials to flow, especially during manufacturing processes like from the hopper to the die (Prescott and Barnum, 2000), and the spherical shape has been indicted to enhance flowability of materials due to a low possibility of fusion as a result of asperitic melting (Tomas and Kleinschmidt, 2009). Therefore, the DMRS blends with more discrete spherically shaped particles will be expected to flow better than the URS blends. The particle size of the blends (Table 1) may also allude to this postulation. Typically, once the percentage of small particles in a bed of granules is high, surface forces like Van der Waal's forces and electrostatic forces can bond the particles together, thus causing an increase in frictional drag, and consequently a reduction in flow (Cameron *et al*, 2005). The particle size ranked DMRS/$L_{2:1}$ > DMRS/$L_{1:2}$ > DMRS/$L_{1:1}$ > URS/$L_{1:2}$ > URS/$L_{2:1}$ > URS/$L_{1:1}$.,thus showing that the blends containing the dual modified rice starch exhibited better flow potentials.

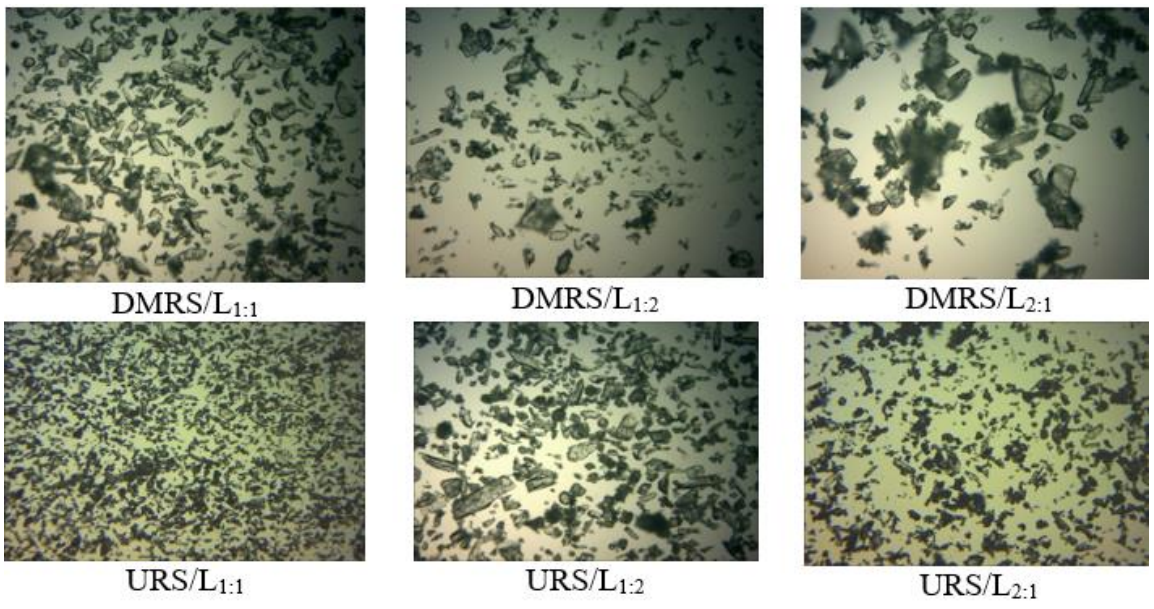

Figure 1: Morphology of the starch blends

Table 1:
Physical properties of granule blends

Sample	Bulk Density (g/mL)	Tapped Density (g/mL)	Hausner's Ratio	Carr's Index (%)	Angle of repose (°)	Particle size (µm)
URS/$L_{1:1}$	0.57± 0.07	0.83± 0.13	1.51± 0.03	33.27± 0.23	28.65± 1.04	11.50 ± 1.31
URS/$L_{1:2}$	0.57± 0.11	0.77± 0.02	1.39± 0.06	27.83± 0.02	31.31± 0.03	19.43 ± 1.31
URS/$L_{2:1}$	0.56± 0.02	0.83± 0.07	1.51± 0.11	37.37± 0.02	31.49± 1.01	12.15 ± 0.18
DMRS/$L_{1:1}$	0.76± 0.14	1.04± 0.04	1.36± 0.06	26.92± 0.37	23.71± 0.05	28.53 ± 1.46
DMRS/$L_{1:2}$	0.69± 0.02	0.91± 0.06	1.32± 0.18	24.17± 0.02	22.80± 0.02	29.02 ± 1.11
DMRS/$L_{2:1}$	0.79± 0.03	1.01± 0.11	1.27± 0.02	21.78± 0.16	26.98± 0.08	39.58 ± 2.37

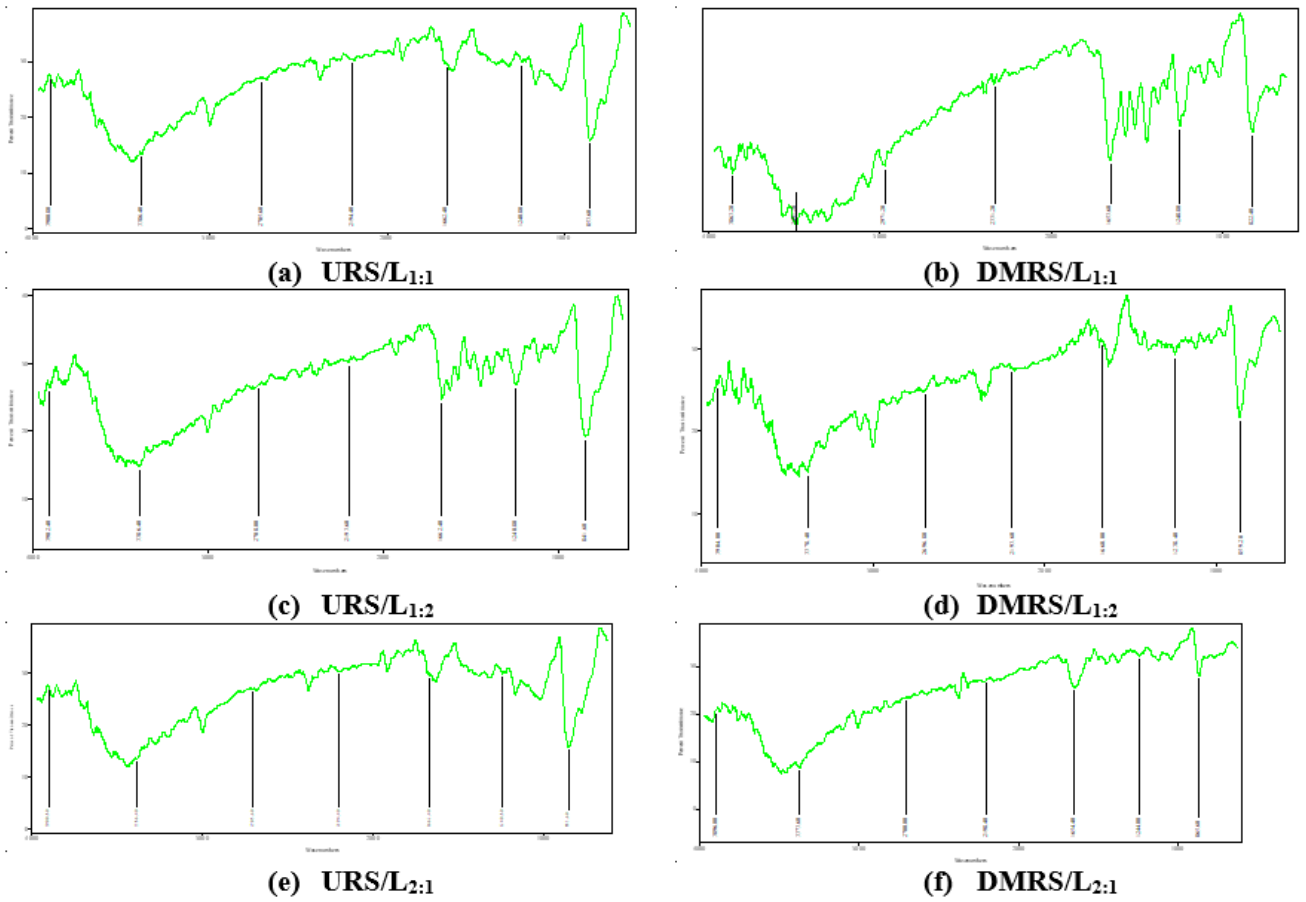

Figure 2:
FTIR plots for unmodified (a,c,e) and dual modified (b,d,f) rice starches

Bulk density measures the quantitative property of a bed of granules, rather than the individual particle, and since the bulk of a bed of granules contains inter-particulate air-filled voids, the bulk density is always less than the particle density (Geldart *et al*, 2006). From Table 1, it can be seen that the DMRS/L blends had higher bulk and tapped density values than the corresponding URS/L blends. Elimination of intrinsic pores due to tapping, which consequently leads to more densification of the powder bed was more pronounced in the URS/L blends. The two flow indices derived from the density measurements (Hauner's ratio and Carr's index) are also shown in Table 1. Though rarely observed, a value of 1 and 0 for Hauner's ratio and Carr's index indicates a bulk solid which is not compressible (Schulze, 2008). Values for Hauner's ratio less than 1.2 indicates a free-flowing bed of particle, 1.2 to 1.35 indicates a moderate flow, while greater than 1.35 and 1.6 indicates a poor flow and cohesive material respectively. Generally, values of the Hausner's ratio for the DMRS/L blends at all ratios can be categorized as having good flow properties, while URS/L blends with values greater than 1.35, but less than 1.6 have poor flow. Among all the samples, only DMRS/$L_{1:2}$ and DMRS/$L_{2:1}$ can be categorized as having good compressibility based on the Carr's indices of 24.17± 0.02% and 21.78± 0.16% respectively.

The angle of repose has also been used extensively to characterize flow based on inter-particulate friction or resistance to movement between particles (Iveson *et al*, 2002). The angle of repose ranked DMRS/$L_{1:2}$ > DMRS/$L_{1:1}$ > DMRS/$L_{2:1}$ > URS/$L_{1:1}$ > URS/$L_{1:2}$ > URS/$L_{2:1}$. It can be inferred that the blends containing the dual modified rice

starch flowed better than the blends containing the unmodified rice starch. The higher the angle of repose, the more cohesive the material is,however, according to Carr's classification, all the batches investigated are free flowing (Al-Hashemi and Al-Amoudi, 2018).

Fourier Transform Infrared (FTIR) spectroscopy was used to monitor changes in the structure of the dual modified (pregelatinized and silicified) rice starches, in comparison with the unmodified rice starch for the different starch-lactose blends studied. The choice of the FTIR in characterising the starches is because of its accuracy, rapid, and relatively sensitive results (Jaggi and Vij, 2006). The FTIR plots are shown in Fig. 2. The FTIR spectrum of URS/$L_{1:1}$ contains characteristic peaks at 853.60 cm^{-3} and 1240.80 cm^{-3}, which are due to strong C-H bends present in aromatic rings and strong C-N stretch due to aromatic amines respectively (Fan *et al*, 2012). The same set of peaks were observed in the FTIR plot for the DMRS/$L_{1:1}$, but now occurring at 822.40 cm^{-3} and 1248.80 cm^{-3} respectively. Other characteristic peaks identified in the FTIR spectrum for URS/L include 1662.40 cm^{-3} attributable to C=O stretching, 2194.40 cm^{-3} (C≡N stretching) and 2705.60 cm^{-3} due to strong C-H stretch of aldehydes (Nandiyanto *et al*, 2017). It was observed that there were slight additions to the functional group integrity of the unmodified rice blend because of the physical modification by pregelatinization and chemical modifications by silicification. This is exemplified by peaks occurring at 2971.20 cm^{-1} (due to C—O—C stretching) which can be attributed to water associated with starch molecules due to pregelatinization (Luo and Shi, 2012). However, the basic integrity of the starch was not compromised when the fingerprint regions of the peaks were observed.

The oral route of administration remains the commonest route of drug administration, while tablets are still the most utilized dosage form (Helliwell and Taylor, 1993). The uniformity of weight and API content verification of the directly compressed tablets showed that all the tablets tested were within the expected range (British Pharmacopoeia, 2002). The mechanical and release properties of the tablets formulated using the different starch blends as excipients are presented in Table 2. Crushing strength and Friability profiles are indications of how resistant a tablet is to external forces that cause abrasion during the process of packaging, shipping and handling. It is also a measure of weakness of a tablet. Table 2 indicates that the crushing strength and friability values have an inverse relationship. Generally the dual modified tablets had higher crushing strength value when compared with tablets containing the unmodified rice-lactose blends, with tablets containing DMRS/$L_{1:2}$ having the highest crushing strength value of 62.38± 1.37 N and the lowest friability value of 0.83± 0.03 %. When rice starch was silicified by co-fusion method, the resulting tablets formulated using the modified starch were more friable than the corresponding tablets containing the unmodified starch (Adetunji and Iorkua, 2020).

Table 2:
Tablet Properties

Granule blends	Crushing Strength (N)	Friability (%)	CSFR	Disintegration Time (secs)	Dissolution Time ($t_{50\%}$) (mins)	Dissolution Time ($t_{90\%}$) (mins)
URS/$L_{1:1}$	44.13± 0.17	4.76± 0.06	9.27	32	8.5	59.7
URS/$L_{1:2}$	47.07± 1.04	2.03± 0.11	23.19	30	8.5	38.6
URS/$L_{2:1}$	48.13± 0.06	3.18± 0.03	15.14	29	9.8	37.3
DMRS/$L_{1:1}$	57.26± 0.14	1.63± 0.14	35.13	20	8.5	56.6
DMRS/$L_{1:2}$	62.38± 1.37	0.83± 0.03	75.16	34	8.2	36.3
DMRS/$L_{2:1}$	58.13± 0.06	1.48± 0.15	39.28	22	7.9	27.4

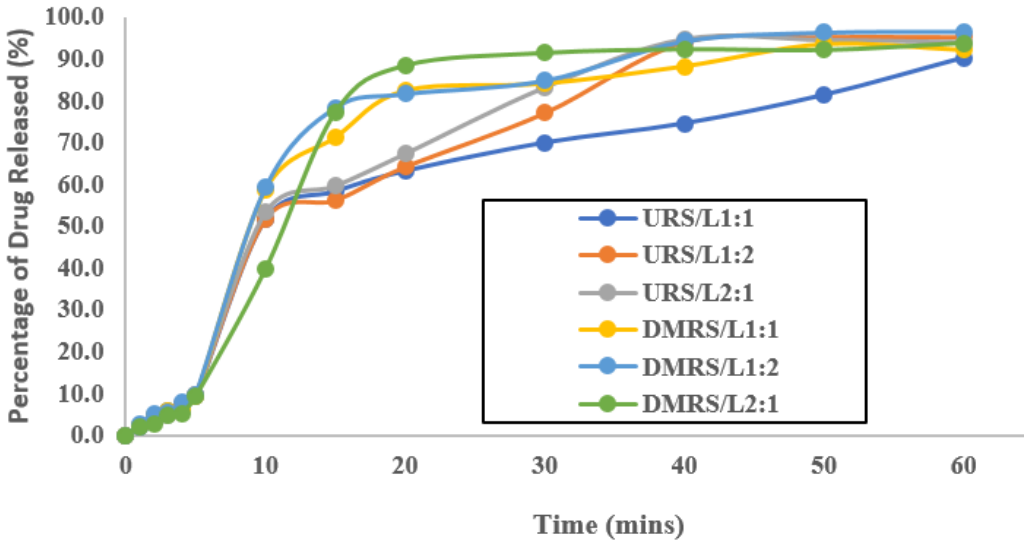

Figure 3:
Dissolution plot showing percentage drug released (%) versus time (mins)

In the current research, pregelatinization prior to subsequent silicification of rice starch led to higher crushing strength values of tablets and the implication of this is that the modification led to formation of tablets that showed more resistance to abrasion when compared with the tablets containing the unmodified starch blends as excipients. The values of the crushing–strength friability ratio also supports this. For the release properties, it was observed that tablets containing the dual modified starches disintegrated and released the API faster. This could be attributed to the enhanced water carrying capacity of the starches due to pregelatinization (Amidon *et al*, 2017) and the introduction of more hydrophilic functional groups due to silicification. Generally, it was observed that there was an initial slow rate of dissolution, up till a period of about 6 minutes, after which the rate became faster. All the tablets containing the dual modified rice starch released more than 70% of the active ingredient within 15 minutes as shown in Fig.3, with the formulation containing DMRS/$L_{1:2}$ having the fastest release rate.

In conclusion, the study shows that dual modification involving pregelatinization and silicification of rice starch led to enhanced functional properties of the native starch when blended with lactose, and showed better tablet qualities when the dually modified blends were incorporated as excipients.

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