

DEVELOPMENT AND CHARACTERIZATION OF A STARCH-EUDRAGIT COMPOSITE AS A NOVEL PHARMACEUTICAL EXCIPIENT

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Abstract

Background: Hybrid polymers with superior functional properties are developed by physical and chemical means to improve the physicochemical attributes of individual components.

Objective: To develop an eudragit-starch hybrid polymer with new physicochemical and functional properties as a potential excipient for drug delivery.

Methods: Composites of eudragit and maize starch were prepared from a homogenous mixture of the two in the following ratios: 1:1, 1:2.5, 1:5, and 1:10. These were characterized by their flowability, hydration capacity, swelling capacity in different pH media (pH 4, 7 and 9.2), moisture sorption at different Relative Humidity values (RH 75, 82 and 100 %) and DSC thermal properties. The analyses were performed in triplicates, and the results were presented as Mean \pm Standard Deviation using Microsoft Excel.

Results: The composites showed an improvement in the flow properties by considering the angle of repose in the order of eudragit: starch thus, 1:1 > 1:2.5 > 1:5 > 1:10 > 0:1. The composites (eudragit: starch) of 1:1 showed higher values of hydration capacity, moisture uptake, and swelling when compared with the primary components and the other hybrids. The general moisture and water uptake of both the primary components and hybrids are in the order 1:1 > 1:2.5 > 1:5 > 1:10 > 0:1. The DSC thermal analysis of the eudragit and starch hybrid (1:1) showed a glass transition, melting and enthalpy of melting different from those of starch and eudragit.

Conclusion: A new Eudragit-Starch (Eu-St) polymer hybrid was formed, showing physicochemical and functional properties that are different from those of the primary components in terms of enhanced flowability, moisture sensitivity and affinity, moisture sorption and swelling capacity that was pH sensitive. Thus, demonstrating the potential for use as a pharmaceutical excipient.

Keywords: Starch, eudragit, hybrid polymer, functional properties, DSC analysis

Introduction

Pharmaceutical excipients are substances besides the active drug included in a drug formulation to aid processing during manufacture or protect, support or enhance stability, bioavailability and patients' acceptability or improve the overall safety and effectiveness of the drug during storage and use [1]. Studies have shown that single-component excipients do not always provide the required performance to formulate some active pharmaceutical ingredients [2]. Several techniques have been explored to produce new excipients by chemical modification of the naturally occurring ones [3]. Hybrid polymers with new physicochemical and superior functional properties have also been developed by physical and chemical modification of polymers which combine the attributes of individual components in terms of their physicochemical properties [3; 4].

Starch, a natural polymer found in green plants, serves multifunctional purposes as an excipient in many conventional drug formulations, such as diluents, binders, disintegrants, and glidants. Native starch has certain limitations, including cold water insolubility, poor flow, low emulsifying power and instability of the gel at various pHs, limiting its application in drug production. Hence the need to develop new starch moieties with better functionalities [5]. Eudragit RL100, also known as amino methacrylate copolymer, is a neutral and inert polymer commonly used for drug production [6]. It is used as a film coating material for solid oral dosage forms to mask taste, control drug release and bioavailability, and formulate nano-particulate drug delivery systems. Several studies have shown the possibility of enhancing the functional properties by modifying some physicochemical

properties [7]. Thus, this study aims to improve the functionality of maize starch by preparing eudragit RL100 and starch composites as a new polymer hybrid pharmaceutical excipient.

Materials and Methods

Materials

Maize Starch, Eudragit RL100 (Röhm GmbH & Co., Germany), buffer solutions (pH 4, 7 & 9.2), pH meter, weighing balance (Mettler Toledo), moisture content analyzer (OHAUS), vortex mixer (QLS; MLS-2500), thermometer (DIGI-SENSE), centrifuge (GFL 1083) and DSC 204 F1 (Phoenix NETZSCH). All other reagents are of analytical grade.

Method

Preparation of starch gel

Maize starch (10 g) was weighed and transferred into a beaker containing 200 ml of 2 N potassium hydroxide solution. This was stirred and heated using a magnetic stirrer (VWR Scientific, USA) to give a clear dispersion. The mixture was adjusted to pH 4 using 2 N hydrochloric acid (HCl). The dispersion was placed in a refrigerator and frozen at -5 °C for 24 hrs, then thawed at 27 °C for three cycles. Afterwards, it was centrifuged at 3000 rpm for 10 mins, and the sediment was collected and dried in the oven at 70 °C. This was pulverized, screened through a 250 µm mesh sieve (US Standard sieve, USA), transferred into an air-tight container and stored in a desiccator.

Preparation of eudragit-starch hybrid polymer

Eudragit-Starch composites were prepared by the casting and solvent evaporation method (Table 1).

Table 1: Composition by the ratio of the different Eudragit-Starch composite moieties.

Formula	Eudragit RL100 (g)	Starch (g)
Starch (St)	0.00	10.00
Eudragit (Eud)	10.00	0.00
Eud:St (1:1)	5.00	5.00
Eud:St (1:2.5)	2.86	7.14
Eud:St (1:5)	1.70	8.30
Eud:St (1:10)	0.91	9.09

The method for preparing starch gel was applied for both starch (5 g), and Eudragit (5 g) prepared separately in 50 mL of 2 N potassium hydroxide solution, stirred and heated to obtain clear solutions. Both solutions were mixed under magnetic stirring for 30 min and then adjusted to pH 4 with 2 N HCl to obtain precipitates. The freeze-thaw cycle was repeated and centrifuged at 3000 rpm for 10 mins, and the sediments were dried, screened and stored in the desiccator. This method was used to prepare the other eudragit-starch ratio mixtures.

Physicochemical Characterization

Bulk and Tapped Densities

Bulk and tapped densities were determined in triplicates using standard methods (USP, 2007). The tapped volume was determined by tapping with a Stampfvolumeter (Sav-2003, Germany), and the densities were calculated as thus;

$$\text{Bulk Density (g/ml)} = \frac{\text{Weight of sample (g)}}{\text{Bulk volume (ml)}} \quad (1)$$

$$\text{Tapped Density (g/ml)} = \frac{\text{Weight of sample (g)}}{\text{Tapped volume (ml)}} \quad (2)$$

Flow Rate

Two grams of each polymer mix was poured into a 2 cm orifice glass funnel mounted on a retort stand. The time taken for the powder to pass through the funnel was noted and performed in triplicates. The flow rate was calculated using eq. (3):

$$\text{Flow Rate (g/s)} = \frac{\text{Mass of powder (g)}}{\text{Average time of flow (s)}} \quad (3)$$

Angle of repose

A glass funnel of 1 cm orifice was clamped 10 cm to the surface. The powder (2 g) was gently poured into the funnel and allowed to flow to form a conical heap. The height and radius (r) of the powder heap were determined. The angle of repose was evaluated using Eq. (4):

$$\text{Angle of repose } \phi (\circ) = \tan^{-1}(h/r) \quad (4)$$

Moisture Content

The percentage moisture content of the composites (2 g) was obtained by placing each in a moisture content analyzer (Ohaus –MB45, Switzerland) and monitored. This was performed in triplicates.

Hydration Capacity (HC)

Each powder (2 g) was weighed into a pre-weighed 15 mL graduated plastic centrifuge tube containing 10 mL of distilled water and agitated on a vortex mixer for 10 mins. They were allowed to stand for 10 mins and centrifuged at 1000 rpm for 10 mins. The supernatant was discarded. The weight of each sample was determined, and the hydration capacity was evaluated using Eq. (5):

$$\text{Hydration Capacity (\%)} = \frac{\text{Weight of hydrated sample (g)}}{\text{Weight of dry sample (g)}} \times 100 \quad (5)$$

Swelling Capacity

Compacts (250 mg - W_d) of the various composite polymers were made using a single punch tablet press (THP-94352, Shanghai Tianxiang) and stored in a desiccator for 48 hrs. Each disc was placed on a glass slab (2 x 2 cm) of known weight, then placed in a petri-dish containing 60 ml of the swelling media (buffer solutions of pH of 4, 7 and 9.2) maintained at 27 °C. At every 10 mins interval, the glass slides and hydrated discs were removed, dried with a blotting paper and weighed (W_t). The swelling capacity (%) was determined using Eq. (6). The test was continued until the hydrated discs reached a constant weight (W_e), and the percentage equilibrium swelling (Q_e) was determined according to Eq. (7):

$$\text{Swelling Capacity (\%)} = \frac{W_t - W_d}{W_d} \times 100 \quad (6)$$

$$\text{Equilibrium Swelling capacity (\%)} = \frac{W_e - W_d}{W_d} \times 100 \quad (7)$$

Moisture sorption

The moisture sorption isotherms of the various eudragit-starch composites were determined by the gravimetric method. The eudragit-starch composites were previously placed in a petri-dish and stored in an oven (105 °C) for 48 hrs to remove residual moisture. Then, each sample (1 g) was placed in an aluminium foil of known weight and placed in different desiccators containing either distilled water (100 % RH), saturated solutions of sodium chloride (\approx 75% RH) or exposed to atmospheric humidity (\approx 82% RH). The powders were weighed at six-hour intervals until a constant (equilibrium). The equilibrium moisture sorption (EMS) was determined using Eq. (8):

$$\text{EMS (\%)} = \frac{M_e}{M_d} \times 100 \quad (8)$$

Where: M_e is the amount of moisture sorption at equilibrium, and M_d is the dry weight of the material (Lin *et al.*, 2005).

Differential Scanning Calorimetry (DSC Analysis)

Thermal analysis was carried out on a DSC 204 F1 machine. Indium (156.8 °C) was used as the internal standard. Approximately 1 mg of starch, eudragit and Eu-St (1:1) were placed in an aluminium pan (25 μ L) and covered with a perforated lid. Dry nitrogen was used as purge gas (purge 20 mL min⁻¹). The probes were heated from a start temperature of 25 °C to 300 °C at a rate of 10 °C min⁻¹. The relevant thermodynamic parameters were noted.

Statistical Analysis

The analysis of the various tests was performed in triplicates and analyzed using Microsoft Excel. The results are presented as Mean \pm Standard Deviation.

Results

Physicochemical Properties

The physicochemical properties of the various polymer blends are displayed in Table 2. An increase in bulk density and flow of the powders were observed when eudragit was added to starch paste (1:1). However, these values decreased as the starch concentration increased. The same observation is made for the tapped density. In addition, a decrease in Carr's index (1:1) was also observed, with a further increase as the concentration of starch increased. However, the composite (1:1) had the lowest angle of repose, and this increased when the concentration of starch increased. The moisture content showed variable values, as shown in Table 2.

Table 2: Physicochemical properties of Starch, Eudragit and Eudragit-Starch composite.

Parameters	Starch	Eudragit	1:1	1:2.5	1:5	1:10
Bulk density (g/ml)	0.34 \pm 0.01	0.42 \pm 0.01	0.87 \pm 0.04	0.65 \pm 0.02	0.41 \pm 0.01	0.36 \pm 0.01
Tapped density (g/ml)	0.61 \pm 0.02	0.71 \pm 0.02	1.11 \pm 0.11	1.05 \pm 0.06	1.00 \pm 0.05	0.65 \pm 0.02
Carr's Index	44.10 \pm 1.48	39.20 \pm 1.20	21.70 \pm 5.02	38.80 \pm 4.66	59.2 \pm 1.83	43.60 \pm 2.11
Hausner's Ratio	1.79 \pm 0.04	1.38 \pm 0.10	1.28 \pm 0.09	1.63 \pm 0.12	2.45 \pm 0.11	1.77 \pm 0.09
Flow Rate (g/s)	1.05 \pm 0.49	1.55 \pm 0.40	2.33 \pm 0.03	1.98 \pm 0.02	1.23 \pm 0.02	1.40 \pm 0.03
Angle of Repose ($^{\circ}$)	36.90 \pm 1.65	32.6 \pm 1.60	26.60 \pm 3.46	30.10 \pm 2.66	31.8 \pm 3.55	33.70 \pm 3.70
Moisture Content (%)	11.70 \pm 0.46	9.70 \pm 0.16	10.15 \pm 3.11	9.37 \pm 0.55	13.55 \pm 0.24	10.43 \pm 0.80

Hydration Capacity (HC)

An increase in HC of composites was observed with the eudragit-starch hybrid (1:1). However, a decrease in HC was observed with the eudragit-starch hybrid (1:2.5). Then, a continuous increase in HC as the concentration of starch increased in the order 1:10 > 1:5 > 1:2.5, as shown in Fig. 1.

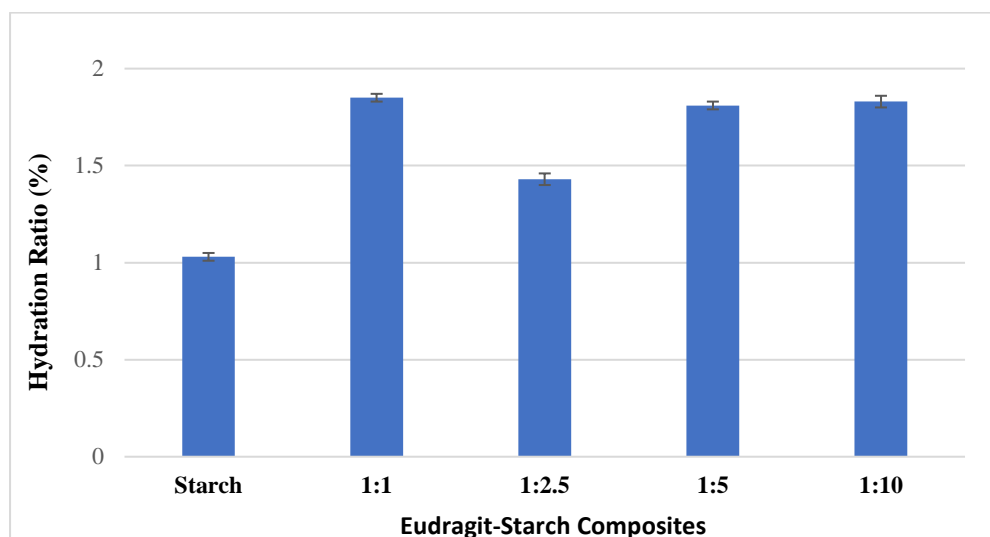


Figure 1: Water retention capacity of Eudragit-Starch composite.

Moisture Sorption

The equilibrium moisture sorption of the starch and eudragit-starch composites showed an increase in sorption as eudragit was added to starch when exposed to all the RH values. Although, a decrease in sorption occurred when the concentration of starch increased, as presented in Fig. 2.

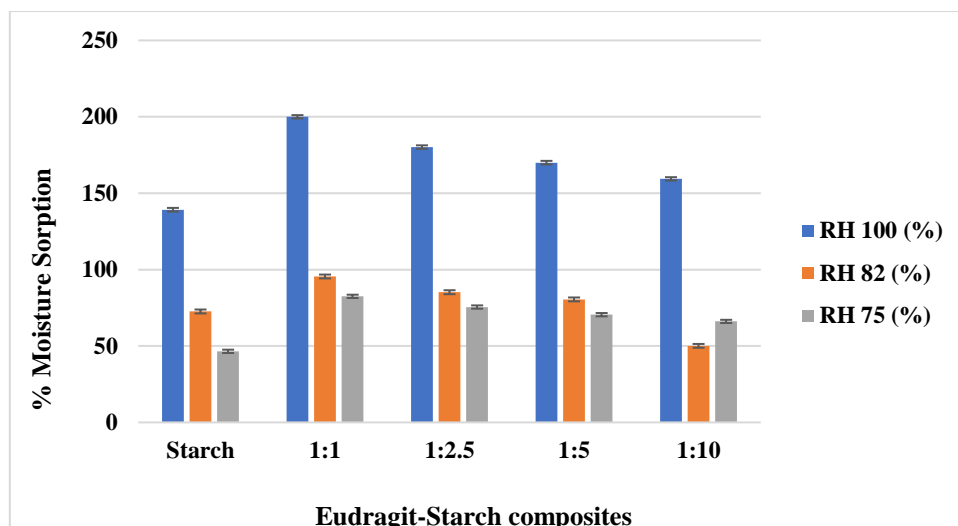


Figure 2: Equilibrium moisture uptake of Eudragit-Starch composites at a different relative humidity

Equilibrium Swelling Capacity

The percentage equilibrium swelling showed remarkable sensitivity to the eudragit-starch hybrids, with the maximum value shown by the eudragit-starch hybrid (1:1) and the lowest by 1:10, as shown in Fig. 3.

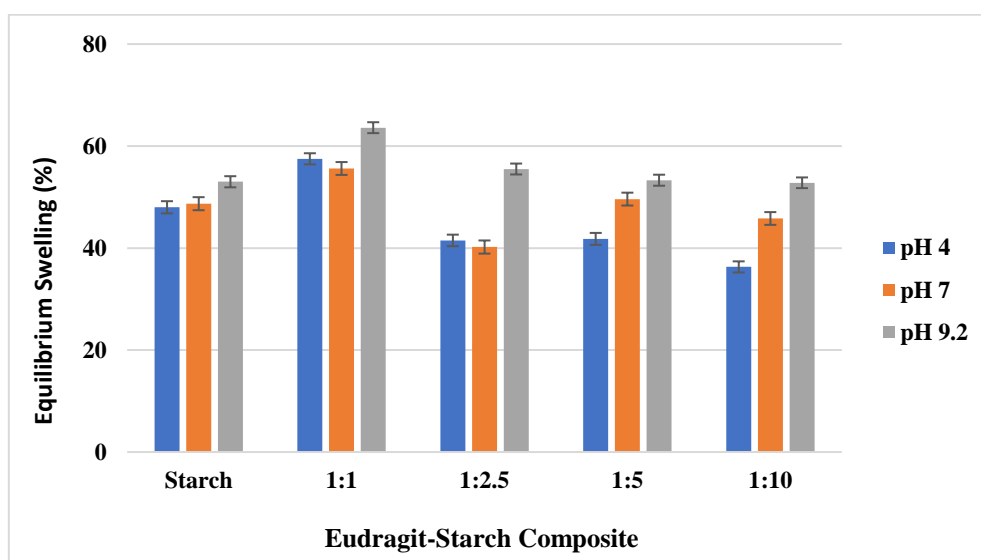


Figure 3: Equilibrium swelling capacity of Eudragit-Starch composites in different pH media

Differential Scanning Calorimetry (DSC) Analysis

The DSC thermograph of starch, eudragit and the eudragit-starch (1:1) composite showed an initial endothermic trough corresponding to the glass transition and an endothermic peak corresponding to their melting transitions. Peak melting temperatures of the hybrid were higher than that of eudragit but less than that of starch, as shown in Table 3.

Table 3: DSC thermal characteristic of Starch, Eudragit and Eudragit-Starch composite.

Parameters	Starch	Eudragit RL100	Eu-St (1:1)
T _g (°C) _{onset}	87.68	97.62	139.75

T_m (°C)	335	242.63 256.42 272.71	320
ΔH (J/g)	14.37	12.94	20.23

T_g – Glass transition temperature; T_m – Melting temperature; ΔH – Enthalpy change

Discussion

The results on the angle of repose for the hybrid composites have good to excellent flow, suggesting an improvement in the flow properties from the parent excipients^[8]. However, the flow characteristics, as shown by Carr's index and Hausner's ratio in terms of hierarchy, were similar to that presented by the angle of repose, which corresponds to the following order 1:1 > 1:2.5 > 1:10 > 1:5 > Eudragit > Starch. The differences in the strength of the flow characteristics in relation to the values can be attributed to the difference in the evaluation method. The moisture content of pharmaceutical powders affects their behaviour during the manufacture of tablets in terms of handling, transportation, and storage^[9].

The maximum allowable limit for moisture content in starch and its derivatives is 14 %, an increase in moisture encourages the growth of micro-organisms that causes odours and changes in flavour^[10]. Although the eudragit-starch blends showed variable moisture content, all fell within the acceptable limits for moisture content. The hydration capacity evaluates the water retention capability and controls the polymer's functionality, especially in drug delivery release characteristics^[11]. Therefore, the eudragit-starch blend showing the highest hydration capacity can be a function of the swelling capacity of the blends^[12].

Moisture sorption has been related to amorphous content and is a predictor of polymers' moisture sensitivity and diffusivity^[13]. Therefore, the highest moisture uptake of the hybrid may be due to the amorphous contents of starch and eudragit to produce a hybrid with relatively higher amorphous content^[14].

In addition, moisture uptake for starch and the composite polymers showed consistent variation with humidity. Swelling affects the mechanical, physicochemical, functional and stability profiles of polymers. The maximum swelling shown by the eudragit-starch hybrid (1:1) indicates that a specific ratio mix of starch and eudragit will produce a hybrid of maximum swelling. The short stability time in media (pH 4) may be related to poor gelation of the polymer due to the ionization of the micro-particles, while the highest stability in media (pH 9.2) may be due to increased gelation due to the formation of a more stable polymer mesh. The pH responsiveness for compact stability and swelling is a fundamental characteristic of a *smart polymer*^[15]. Vasile *et al.*^[16] noted that hybrids made of natural and synthetic polymers usually had enhanced physicochemical properties. In addition, the starch-carboxymethyl cellulose hybrid developed by Cagnin *et al.*^[17] showed increased swelling capacity that was pH sensitive and noted that these properties are excellent in drug delivery systems.

The DSC thermal analysis is an essential tool used to evaluate the effect of temperature changes/time on the behaviour of polymers. It also reveals delicate and more subtle changes within the polymer matrix, like the glass transition^[18]. The glass transition and melting temperatures for the starch, Eudragit and hybrid polymers differ in values which agrees with^[19]. The higher enthalpy change shown by the hybrid indicates that more energy is required to break the bonds in the hybrid polymers. This can be due to several factors, such as the relationship between the enthalpy and entropy^[20], morphology, composition and types of bonds present within the polymers, cross-linking, and the effects of plasticizer^[21].

Conclusion

A new Eudragit-Starch (Eu-St) polymer hybrid was formed. It exhibited physicochemical and functional properties that are different from that of the primary components, in terms of enhanced flowability, moisture sensitivity and affinity, moisture sorption and swelling that was pH sensitive. The new relative glass transition, melting; and enthalpy also corroborate the formation of a new hybrid polymer with potential stability superior to the primary components. The new eudragit-starch hybrids can be employed in a drug delivery application as a drug carrier for controlled and target drug release and as a disintegrant.

Conflict of interest

The authors declared no conflict of interest.

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