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Preparation and Characterization of Starch Microparticle for Drug Release Systems

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Abstract

This work was designed to produce starch microparticles that would be used as controlled drug released carriers. Crosslinked and non-crosslinked starch microparticles were prepared by the water-in-oil emulsion solvent diffusion method. Sodium trimetaphosphate and methylene blue were used as the crosslinking and the water-soluble drug model respectively. Crosslinked and non-crosslinked starch microparticles were characterized by their micromeritic properties (size, density and angle of repose) and liquid uptake ability. From the results both the crosslinked and non-cross-linked starch microparticle demonstrated size homogeneity of 500-1000µm with % swellabilty of 28.57% which was highest in the non-crosslinked starch microparticles while the crosslinked starch microparticles gave a percentage swellability of 25%. Crosslinking can be said to reduce percentage swellabilty. The results from the angle of repose indicated that the powders of the crosslinked starch microparticles which has angle of repose of 24.90° had an excellent flow property while the non-crosslinked starch microparticles which has angle of repose of 33.70° had a good flow property.

1.0 Introduction

These days owing to busy and sedentary lifestyle, people are affected by a number of fatal lifestyles associated diseases [1]. Majority of such diseases require prolonged, even lifelong treatments resulting in the use of multiple daily drug dosing. This can be inconveniencing. Therefore, numerous researches are being conducted on controlled drug release agents that can release drug for overlong period, thereby reducing the number of daily doses [2, 3]. During the past few decades, natural biopolymers have been frequently used as functional excipients in designing drug delivery systems of diverse kinds owing to their excellent biocompatibility, and biodegradability [4]. The development of biocompatible polymeric microparticles for controlled release drug delivery applications has been a subject of great interest for the past few decades [5, 6]. Controlled drug delivery technology represents one of the frontier areas of science, which involves multidisciplinary scientific approach, contributing to human healthcare [7]. These delivery systems offer numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity, and improved patient compliance and convenience. Microparticles, microspheres, and microcapsules are common constituents of multiparticulate drug delivery systems offering numerous advantages based on their structural and functional abilities [8], and their application is suitable for convenient and tolerable drug administration through several routes. Depending on the

formulation, they can be incorporated into different pharmaceutical dosage forms such as solids (capsules, tablets, sachets), semisolids (gels, creams, pastes), or liquids (solutions, suspensions, and even parenterals). The major challenge in the treatment of diseases especially the treatment of ulcerative colitis is appropriate local targeting and drug related side-effect [9]. The main purpose of using drug delivery systems is as implied not only to deliver a biological active compound in a controlled manner (time period and releasing rate) but also to maintain drug level in the body within therapeutic window. Besides, one can direct the drug towards a specific organ or tissue (targeted drug delivery) [4]. Microparticles including both microcapsules and microspheres are generally fine spheres usually less than 1000 μm in diameter [10]. Microspheres can have homogeneous drug distribution throughout the polymer matrix. Alternatively, a drug can be captured inside a polymer coating creating a reservoir system (also called microcapsules). One more type of microparticles includes a drug adsorbed onto the particle surface by the means of different applications such as physical, ionic, or chemical interactions [10]. Microparticle-based formulations can increase the stability of drugs, enzymes to be delivered and released in a sustained manner at the target site [11]. In the past few decades, microparticles for parenteral applications were mainly investigated as a controlled release drug delivery carrier, and they were all were based on biodegradable polymers. The term "microcapsule" is defined, as a spherical particle with the size varying in between 50nm-2mm containing a core substance. Microspheres are instrict sense, spherically empty particles [7]. However, the terms microcapsules and microspheres are often used synonymously. Still, [7] stated that some related terms are used as well. For example, "microbeads" and "beads" are used alternatively. Sphere and spherical particles are also employed for a large size and rigid morphology. In the pharmaceutical industries the use of natural biodegradable polymers as controlled drug delivery carriers will enhance drug delivery services because the major components or ingredients present are natural, also they are biodegradable which will reduce the risk or adverse effects of synthetic drug delivery carriers. This work is intended to use natural bio-degradable starch polymer to produce crosslinked and non-crosslinked starch microparticles as controlled drug delivery carriers.

2.0. Materials and methods

2.1 Preparation of starch microparticles and crosslinked starch microparticles

All the reagents used in this study were of analytical grade.

The 20% (w/v) starch solution was prepared by using 2% (w/v) NaOH solution as the solvent. Starch microparticles were prepared by the water in oil emulsion solvent diffusion method [12]. In a typical reaction for crosslinking the starch 1.0g of sodium trimetaphosphatewas reacted with 10.0g of starch solution before dissolving 0.5g methylene blue into it with stirring to completely homogenize the mixture. 1.0mL of the crosslinked starch was added drop-wise into 100ml of ethyl acetate containing 5% (w/v) of Span 80 and Tween 80 mixture (Span 80/Tween 80 = 90.65/9.35w/w) in a beaker with a stirring at a speed of 900rpm for 1hr. The beaker was tightly sealed with aluminum foil to prevent evaporation of ethyl acetate during the emulsification-diffusion process. The starch microparticles suspended in ethyl acetate were collected by centrifugation before rinsing it three times with fresh ethyl acetate and drying in a vacuum oven at room temperature overnight.

2.2 Characterization of the Starch Microparticles

Swelling capacity [13]. The experiment was carried out in a 100ml graduated cylinder. The initial bulk volume (v_d) of 1.0g each of the starch microparticle sample (crosslinked and non-crosslinked starch microparticles) were noted and distilled water was added till the 100ml mark to yield a 100ml uniform dispersion. The sediment volume (v_s) of the swollen mass at each 6hours intervals at room temperature and the % swellability was calculated using equation (1).

$$\% \text{ Swellabilty} = \frac{V_s - V_d}{V_s} \times 100 \quad (1)$$

Where V_s = volume of swollen starch microparticles and V_d= volume of dry starch microparticles

For the swelling capacity ethanol was used instead of water, but all other parameter remained the same.

Angle of repose [14]. This involves formation of pile of the powdered material on a flat platform by suspending the powder through a funnel. The height of the pile (h) was kept fixed for convenience. The radius (r) of the pile was then measured. Finally, using equation (2), the angle of repose was calculated.

$$\theta = \tan^{-1}\frac{h}{r} \quad (2)$$

Where h = height of the microparticles pile and **r** = radius formed by the microparticles pile.

Bulk density determination [13]. The bulk density of the powder bed is the weight of the powder divided by the whole volume of the microparticle bed. 10g each of the powders crosslinked and non-crosslinked were poured inside a measuring cylinder made of glass through a funnel at zero pressure. The bulk density was calculated using equation (3).

$$\text{Bulk density} = \frac{\boldsymbol{weight\ of\ powder}}{\boldsymbol{whole\ volume\ of\ the\ bed}} \quad (3)$$

Tapped density [15]. It was determined using the bulk density apparatus. 10g of microparticles were put in a 100ml measuring cylinder and the initial volume (v_b) noted. The measuring cylinder was then tapped till no further change in volume was observed (v_t). Tapped density was calculated using the equation (4).

$$\text{Tapped density} = D_t = \frac{m}{V_b - V_t} \quad (4)$$

Where D_t = tapped density,
M = mass of granules,
V_b= bulk volume of granule,
V_t = tapped volume of granules,
The carr's compressibility index was calculated using the equation (5).

$$\text{Carr's index (\%)} = \frac{D_t - D_b}{D_t} \times 100 \quad (5)$$

Where D_t = tapped density and
D_b=bulk density,
Hausner ratio was calculated using the equation (6).

$$H = \frac{D_t}{D_b} \quad (6)$$

Where D_t = tapped density and
D_b=bulk density,
The crosslinked density of the starch microparticles were calculated using the Flory's equation:

$$Q = \frac{V_t(swollen\ polymer)}{V_t(dry\ \ polymer)} \quad (7)$$

The particle size distribution of the starch microparticles were checked using a calibrated microscope.

3.0. Results and Discussion

3.1 Particle size distribution

The average size of microparticles can be estimated by determination of their diameters [18]. The crosslinked starch microparticles samples presented a size distribution of (500-1000μm) with the mean average of 667μm while the non-crosslinked starch microparticles presented a size distribution of (500-1000μm) with a mean average of 830μm. The crosslinked starch microparticles were smaller in size than the non-crosslinked starch microparticles because of the presence of the crosslinking in them. These particle size features can be related to some homogeneity of the material so that when stress is applied in comminuting process the fissures are distributed in a somewhat homogenous manner throughout the fragile points of polymer network [16]. Faster swelling rate and larger equilibrium swelling are observed as particle size increases or the microparticle size diminishes [17]. The swelling capacity of the non-crosslinked starch microparticles is more than those of the crosslinked starch microparticles. This is owing to the fact that the crosslinked starch microparticles contained more starch than non-crosslinked starch microparticles. Particle size especially microparticles with a size range of 0-1000μm is hydrophilic and biodegradable thereby any microparticle in the size range of 0-1000μm swells so easily [17]. The particle sizes of microparticles are also dependent on its specific use. For example, in designing of appropriate inhaled carrier systems with adequate aerodynamic characteristic for pulmonary drug delivery the size of the particle is critical. The carrier particle should be small enough to reach the affected site but not so small that they fail to be ineffective.

3.2. Swelling capacity

The swelling degree is an important property to be evaluated in hydrophilic polymers used in controlled drug delivery systems because it is correlated with the diffusion rates of the penetrant into the matrix [19]. Besides, structural changes due to crosslinking and the drug release behaviour of different materials can be evidenced by their swelling behaviour [16]. The values of liquid uptake (%) in media distilled water; ethanol are showed in Figure 1 and Figure 2 respectively, in which it is seen that the non-crosslinked starch microparticles presented the highest swelling abilities than the starch microparticles of the crosslinked starch. The non-crosslinked starch microparticles exhibited the highest swelling degree, since the hydrophilic polymer (starch microparticles) is in greater proportion, favoring the swelling [19]. The lower swelling ability of crosslinked starch microparticles can be attributed to the high cross-link density of the starch microparticles, such that the mesh size of polymer network limits the water entrance in the polymer structure. Besides, the inter-chains ester linkages of crosslinked samples can restrict the motion of chains affecting the liquid diffusion through them [20].

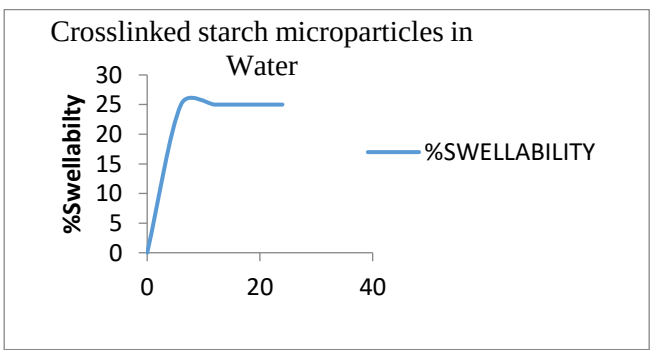

Figure 1: % swellability against time for the crosslinked starch microparticles in distilled water

From Figure 1, it can be seen from the graph that the % swellabilty plotted against time (hrs), that the crosslinked starch microparticles, when immersed in distilled water swell in the first 6hrs reaching a maximum at about 25% swelling. Therefore, it can be said that % swellability of the crosslinked starch beads swells (increased) as the time increased.

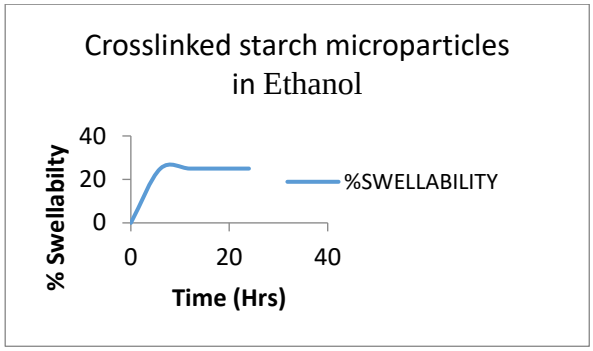

Figure 2: % swellability against time for the cross-linked starch microparticles in ethanol.

It can be seen in Figure 2 that the cross-linked starch microparticles, when immersed in ethanol swelled to a % swellabilty of 25% after 6hrs and thereafter it leveled up. Here, there is no difference in the swelling of the cross-linked and non-crosslinked starch microparticles in distilled water and ethanol due to their close pH values (pH of distilled water = 7.0 and pH of ethanol = 7.4).

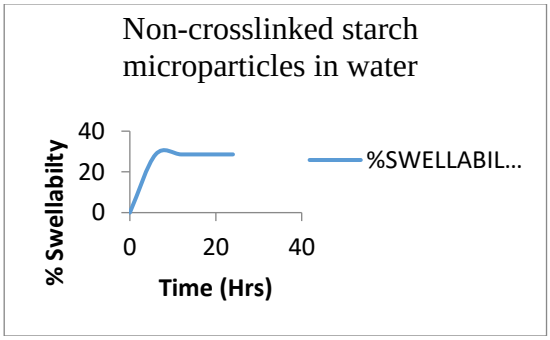

Figure 3: % swellability against time for the non-crosslinked starch microparticles in distilled water.

From the graph on Figure 3, it can be seen that the non-crosslinked starch microparticles, when immersed in distilled water was seen to swell to a % swellability of 28.57% and the swelling occurred within the first 6 hours of immersion into the distilled water, thereafter the microparticles did not swell any further. This shows that the swelling was faster and higher than in the crosslinked starch microparticles.

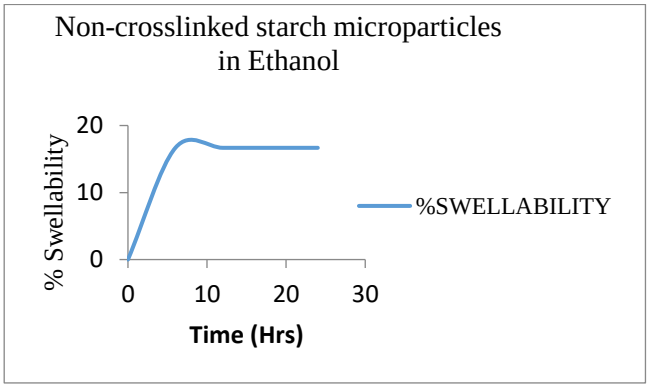

Figure 4: % swellability against time for the non-crosslinked starch microparticles in ethanol

It can be seen that the crosslinked starch microparticles, when immersed in ethanol it is seen to swell to a % swellability of 16.67% and this swelling takes place within the first 6 hours thereafter it does not swell further.

Crosslinked density: According to the equilibrium swelling theory, a polymer will absorb solvent until the solvent chemical potentials in the polymer phase and in the free solution are equal. The amount of water sorption is quantified by the degree of swelling: the ration of the swollen polymer volume or mass to that of the dry polymer [19]. The volume degree of swelling of crosslinked polymers is simply the inverse of the polymer volume fraction so the volume degree can be readily predicted as a function of polymer-solvent interaction parameters, crosslinked density and polymer ionic content [23].

Table 1: Crosslinked densities of the microparticles

	Crosslinked Density (ml/m^3)	
Starch microparticles	In water	In ethanol
Crosslinked	1.33	1.33
Non-crosslinked	1.40	1.20

From the results of the cross-linked density which is influenced by the rate of volume change, it was seen that the crosslink density of the non-crosslinked starch microparticles with the value of 1.40 was higher than the value of the Crosslinked starch microparticles in water. Also, the value of the crosslinked starch microparticles in ethanol which was 1.33 was higher than the value of the non-crosslinked starch microparticles in ethanol which gave a value of 1.20. It can be seen that the crosslinked densities of the crosslinked starch microparticles were less dependent on the medium for increase in volume while the non-crosslinked starch microparticles were more dependent on the medium for increase in volume.

Apparent Densities: The density of a powdered solid influences the flow, so that denser powders present better flow properties [21]. This is because density affects compressibility of powders; the denser the powders the more the flowability and the more easily compressed are the powders.

Table 2: Properties of the powders of the cross-linked and the non-crosslinked starch microparticles.

Microparticles	Angle of repose (^{o})	Bulk density (g/ml)	Tapped density (g/ml)	Hausner ratio	Compressibility index (%)
Crosslinked starch microparticles	24.90	0.40	0.50	1.25	25.00
Non-crosslinked starch microparticles	33.70	0.43	0.47	1.11	11.10

Bulk density is the mass per unit volume of a loose powder bed. The unit volume includes the spaces between the particles themselves. The method used to fill the material into it volume can affect the degree to which the powder is compressed and can thus influence the bulk density value which is

used in determining the amount of powder that can fit in space such as a blender or a hopper on a tablet press or capsule filler. It is also used to determine the amount of powder that can be used in a capsule [22].

The bulk density of the crosslinked starch microparticles is 0.40g/ml while the bulk density of the non-crosslinked starch microparticles is 0.43g/ml. From the values, the crosslinked starch microparticles is better powder for compressing into tablet.

Hausner ratio: From the values obtained it can be seen that the crosslinked starch microparticles of 1.25 showed a fair flow property while the non-crosslinked starch microparticles showed an excellent flow property of 1.11.

Carr's compressibility index: From the values obtained it can be seen that the non-crosslinked starch microparticles showed a value of 25% which is a passible flow property.

Angle of repose: The angle of repose is a parameter that describes the flow ability of materials [21]. From the values in Table 1, it can be seen that the crosslinked starch microparticles presented a repose angle of 24.90^{o} which is an excellent flow property of property of powders while the non-crosslinked starch microparticles gave a value of 33.70^{o} which is a good flow property of powder.

The results of repose angle indicates that, generally, the samples both the crosslinked and the non-crosslinked starch microparticles presented free flowing behaviour, while the highest angle of repose value of non-crosslinked starch microparticles 33.70 demonstrated it can flow less than the crosslinked starch microparticles.

4. Conclusion

The starch microparticles crosslinked with sodium trimetaphosphate and the non-crosslinked starch microparticle were successfully prepared by the water in oil emulsion solvent diffusion method.The results showed that both the crosslinked and the non-crosslinked starch microparticles swelled when immersed in distilled water and ethanol. The microparticles can be used as controlled drug delivery carriers, since they both swell in liquids. Although the non-crosslinked starch microparticle which contains more starch content swelled the highest, also the % swellability is greater in water than in ethanol. Also, from their good flow properties the crosslinked and the non-crosslinked starch microparticles can be used as controlled drug delivery carriers.

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