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# Encapsulation altered starch digestion: Toward developing starch-based delivery systems

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ABSTRACT

Starch is an abundant biomaterial that forms a vital energy source for humans. Altering its digestion, *e.g.* increasing the proportions of slowly digestible starch (SDS) and resistant starch (RS), would revolutionize starch utility in addressing a number of health issues related to glucose absorption, glycemic index and colon health. The research reported in this article is based on my hypothesis that water channels present in the B-type starch crystalline matrix, particularly in tuber starches, can embed guest molecules such as nutraceuticals, drugs, flavor compounds and vitamins leading to altered starch digestion. Toward this goal, potato starch has been chosen as the model tuber starch, and ibuprofen, benzocaine, sulfapyridine, curcumin, thymol and ascorbic acid as model guest molecules. X-ray powder diffraction and FT-IR analyses clearly suggest the incorporation of guest molecules in the water channels of potato starch. Furthermore, the *in vitro* digestion profiles of complexes are intriguing with major variations occurring after 60 min of starch digestion and finally at 120 min. These changes are concomitantly reflected in the SDS and RS amounts, with about 24% decrease in SDS for benzocaine complex and 6% increase in RS for ibuprofen complex, attesting the ability of guest molecule encapsulation in modulating the digestion properties of potato starch. Overall, this research provides an elegant opportunity for the design and development of novel starch-based stable carriers that not only bestow tailored glucose release rates but could also transport health promoting and disease preventing compounds.



## 1. Introduction

The prevalence of diabetes mellitus (DM) is currently affecting 366 million people worldwide, and its proliferation of three new cases every 10 s is projected to affect about 552 million by the year 2030 (http://www.diabetesatlas.org/). The most prevalent form of DM is type 2 diabetes mellitus (T2DM), which is characterized by the combinations of chronic hyperglycemia, insulin resistance and failing β-cell functionality (LeRoith, 2002; Zimmet, Alberti, & Shaw, 2001). Individual's age and obesity in association with sedentary lifestyles contribute most to this multifactorial disease. Its incidence accounts for six mortalities every minute globally (Wild, Roglic, Green, Sicree, & King, 2004) by triggering kidney failure, nerve damage, cardiovascular disease and stroke. Furthermore, it appears elevated in younger children (Alberti et al., 2004; Venkataraman, Nanda, Baweja, Parikh, & Bhatia, 2004) and certain ethnic groups (Mokdad et al., 2001), and is estimated to increase by about 90%, in the near future, in some underdeveloped regions (http://www.diabetesatlas.org/). The total direct and indirect costs associated with this ailment make it one of the most expensive; *e.g.* in the US during 2007, the spending was $174 billion (Petersen, 2008) and the average medical expenses of a diabetic person is 2.3 times higher than those for non-diabetic individuals. Thus, measures to alleviate the T2DM burden are of economic and social significance.

Starch is one of the abundant plant products available to mankind as a major daily caloric intake. It is relatively inexpensive and serves as a vital energy source in several staple food materials as well as ingredients incorporated in foods. As one of the main contributing factors of T2DM is the elevation of glucose level in blood, developing food products with controlled starch digestion will certainly be a positive step in abating T2DM progression and prevention with minimal cost. Starch is generally classified as combinations of rapidly digestible starch (RDS), slowly digestible starch (SDS), and resistant starch (RS) so as to differentiate its digestion in food products and define nutritional perspectives. RDS is digested and absorbed quickly in the small intestine leading to faster accrual of blood glucose. On the other hand, SDS is ingested slowly as glucose is released in a sustained manner, and RS, acting as a dietary fiber, ferments in the colon without assimilating in the upper gastrointestinal track. Thus, altering starch digestion, by manipulating SDS and RS proportions, significantly addresses T2DM issues as well

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as health concerns, such as glucose absorption, glycemic index and colon health (Englyst, Vinoy, Englyst, & Lang, 2003; Jenkins et al., 2002; Wolever, 2003).

Starch is mainly composed of two biopolymers amylose and amylopectin (Buleon, Colonna, Planchot, & Ball, 1998; Wang, Bogracheva, & Hedley, 1998) with D-Glc$_p$ sugars as the monomers; amylose corresponds to a simple linear molecule with covalently linked α (1 → 4) units, whereas amylopectin is highly branched having both α (1 → 4) and α (1 → 6) linkages. The intricate organization of these two molecules results in relatively water insoluble granules that possess alternating amorphous and semicrystalline regions of 100–400 nm thickness. The research reported in this article examines the use of naturally available crystalline arrangement of starch as a matrix to encapsulate relevant small molecules and thereby regulate starch digestion. The hypothesis is that water channels present in the starch matrix, particularly in tuber starches as in potato starch, can embed nutraceuticals, drugs and vitamins, such that the resultant complexes will have modified starch digestion behavior. Among the three known starch types A (cereal), B (tuber/root) and C (mixture of A and B), B-type possesses interhelical water channels. Starches with relatively short average chain lengths of amylopectins yield A-type granules as in waxy maize, rice and wheat; whereas those with long-branch chains correspond to B-type granules as in potato, cassava and high amylose maize, and starches with intermediate amylopectin chain lengths correspond to C-type *e.g.* pea starch. Crystal structure analysis reveals that A- and B-starches adopt similar double helical structures but their packing arrangements are different. Tightly packed networks with 1/3 water molecule per monosaccharide or 4 water molecules/unit cell is a characteristic of A-starches (Imberty, Chanzy, Perez, Buleon, & Tran, 1988), whereas B-starch network contains 3 water molecules per monosaccharide or 36 water molecules/unit cell (Imberty & Perez, 1988; Takahashi, Kumano, & Nishikawa, 2004). The ordered arrangement of water molecules in B-starches results in channels suitable to embed, protect and deliver molecules of interest. Herein, potato starch has been chosen as the model B-starch, and three drug molecules (ibuprofen, benzocaine, sulfapyridine), one nutraceutical (curcumin), one flavor compound (thymol) and one vitamin (ascorbic acid) as model systems. There are several reports on incorporating similar guest molecules in starches by destabilizing the ordered network (Conde-Petit, Escher, & Nuessli, 2006; Gidley & Bociek, 1988; Heinemann, Conde-Petit, Nuessli, & Escher, 2001; Itthisoponkul, Mitchell, Taylor, & Farhat, 2007; Le Bail, Rondeau, & Buleon, 2005; Nuessli, Putaux, Le Bail, & Buleon, 2003; Putaux et al., 2008; Rondeau-Mouro, Le Bail, & Buleon, 2004; Wulff, Avgenaki, & Guzmann, 2005). In contrast, research reported in this communication utilizes the natural crystalline arrangement of B-starches itself for this purpose. Prepared complexes have been characterized by X-ray powder diffraction and FT-IR, and starch digestion is estimated using the Englyst protocol. The results suggest that encapsulation in the starch network indeed alters the SDS and RS amounts.

## 2. Materials and methods

### 2.1. Materials

Potato starch, ibuprofen, benzocaine, sulfapyridine, curcumin, thymol and ascorbic acid were from Sigma-Aldrich. Waxy maize starch was from Tate & Lyle. Reagent grade isopropanol and double distilled water were used as necessary.

### 2.2. Preparation of starch: small molecule complexes

As the chosen small molecules (also termed as guest molecules in the subsequent discussion), except ascorbic acid, are water insoluble, isopropanol was used as a solvent. Solutions were prepared by dissolving 100 mg of solute in 95 mL of alcohol, at room temperature, and later 5 mL of distilled water was added. Experience with polysaccharide fibers suggests that water addition loosens the network and effectively facilitates the diffusion of small molecules (Janaswamy & Youngren, 2012; Janaswamy, Gill, Campanella, & Pinal, 2013). 1000 mg of potato starch was suspended in the alcohol:water:solute mixture and the sealed beaker was left at room temperature in a dark room for one week, after which the complex was filtered out, air dried and equilibrated at 44% relative humidity for further use. The experiments were also performed with waxy maize starch, an A-starch, so as to highlight the importance of water channels of B-starches for encasing molecules of interest. In addition, potato and waxy maize starches were treated with 95% isopropanol as a control. In the subsequent discussion, complex represents guest molecules encapsulation in the starch matrix.

### 2.3. X-ray powder diffraction

About 500 mg of starch samples was packed in an aluminum holder and mounted on a Philips PW 3170 diffractometer interfaced to a personal computer equipped with Automated Powder Diffraction (APD) software. Diffraction patterns were collected at room temperature using Ni-filtered CuKα (λ = 1.5418 Å) radiation with X-ray tube operated at 40 kV and 25 mA. Intensity data were obtained in the diffraction angle 2$\theta$ range 8–38° in a step scan mode with 0.01° step width and 5 s collection at each step. The patterns were smoothed for further analysis by PC-APD (version 3.6) software that resulted in 375 data points. In order to calculate the crystallinity of each starch sample, 200–250 data points in the non-peak regions were selected as background intensities and a ninth-order polynomial was fitted using OriginPro 8.6.0 (Academic) for generating the background intensity profile. Background intensity at each measured data point in the diffraction angle (2$\theta$) was estimated using cubic spline interpolation methodology. Later, the generated background profile was scaled such that it abuts the starch pattern, and the area of crystalline portion was estimated by subtracting the area of background intensity from whole diffraction. Finally, ratio between crystalline fraction to the total area yielded the crystallinity index and was expressed in percentage value.

### 2.4. Fourier-transform infrared spectroscopy (FT-IR)

Spectra of starch, small molecules and starch complexes were collected using a Bio-Rad FTS 6000 Spectrometer (Bio-Rad Laboratories Inc., Philadelphia, Pennsylvania). The scan range was set from 500 to 4000 cm$^{-1}$ and a total of 256 scans at 2 cm$^{-1}$ were co-added for each spectrum.

### 2.5. Digestion properties

The *in vitro* digestibility of potato starch and starch complexes, without cooking, was measured according to the protocol described by Englyst, Kingman, and Cummings (1992) with some modifications. In brief, 550 mg of starch or starch complex was suspended in 50 mL of a solution containing 50 mg of guar gum, stabilized at 37 °C in a water bath and an enzyme preparation that included pancreatin (4.5 g in 30 ml) and amyloglucosidase (3.9 ml) was added. During digestion, 250 μl aliquots were removed at 2, 5, 10, 15, 20, 30, 60, and 120 min and mixed with 2 volumes of anhydrous ethanol. The mixtures were used as stock solutions for glucose measurement. The GOPOD procedure was conducted using an assay kit

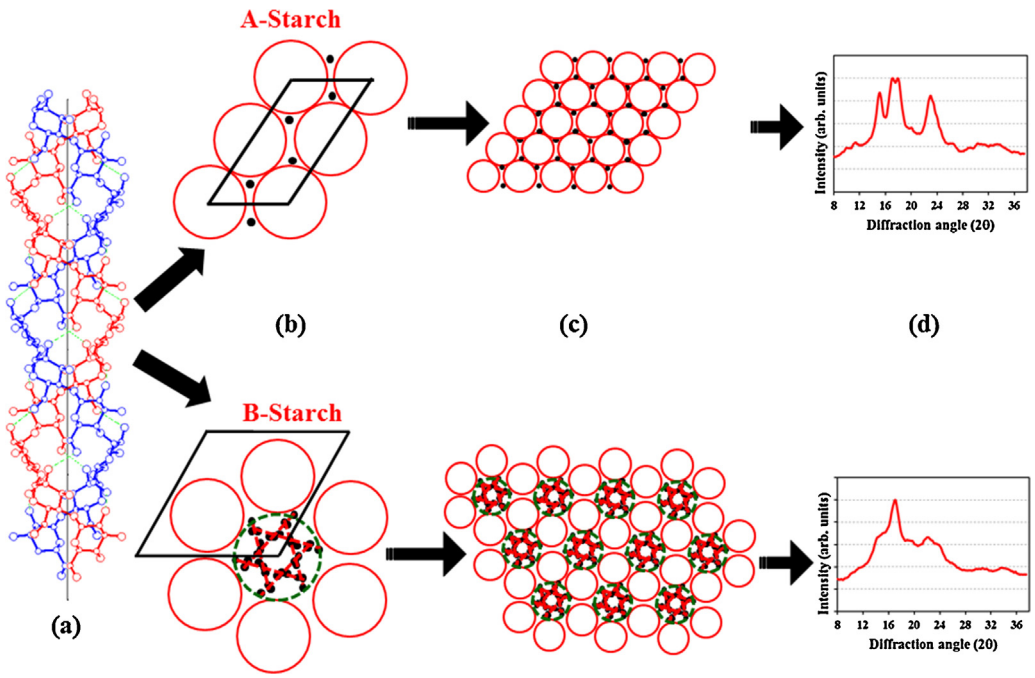


**Fig. 1.** Cartoon highlighting the A- and B-starch packing arrangements and corresponding powder diffraction patterns. (a) The two chains in the starch double helix are held together by inter-chain hydrogen bonds (broken lines in green). This arrangement prevails for both A- and B-starch structures with subtle changes in the conformation angles and helix pitch. The black vertical line represents the helix axis. (b) Projection of the packing arrangement viewed down the helix axis. Each double helix is represented by a circle. The filled black spheres are water molecules. The helices are held together by inter-double-helix hydrogen bonds as well as water molecule mediated interactions. Localization of water molecules in a channel (dashed green circle) is the highlight of B-starch packing, and the dashed red lines signify hydrogen bonds among water molecules. (c) Starch network formation though the association of several unit cells. (d) X-ray powder diffraction patterns of A- and B-starches in the diffraction angle range 8–38°. The differences among the packing arrangements result in the change among A- and B-starch diffraction patterns, and A-starch with sharper well-defined profiles is comparatively more crystalline than B-starch. (For interpretation of the references to color in this text, the reader is referred to the web version of the article.)

(Megazyme) to measure the glucose concentration. Average values from duplicate measurements are reported.

## 3. Results

### 3.1. X-ray analysis

The strategy was to embed guest molecules in the well-organized water-channels of B-starch granules. Isopropanol was used as solvent to transport molecules into the water channels. X-ray diffraction is the best available experimental tool to unravel structural changes at the atomic level upon encapsulation. As starch samples are powdery, X-ray powder diffraction protocols have been used to characterize the prepared complexes. Fig. 1 contrasts the packing arrangements of A- and B-starches and the corresponding diffraction patterns. A-starch helices are close packed, whereas voids filled with clusters of water molecules exist in B-starch granules. Such arrangements bring out substantially different diffraction patterns: relatively well-resolved peaks are characteristics of A-starches, while less crystalline peaks signify B-starches.

The diffraction patterns of potato starch (PS) and its complexes with ibuprofen, benzocaine, sulfapyridine, curcumin, thymol and ascorbic acid are more crystalline (Fig. 2a) than the native starch and do not match with the patterns of the starting small molecules. In PS, the profiles are broader with maximum peak intensity occurring at 16.9 of $2\theta$ followed by less intense peaks at 21.8, 30.2 and 33.3°. The estimated crystallinity is very low at 13%. On the other hand, complexes display new and intense peaks at about 9.8, 11.2, 14.1, 14.9, 17.0, 19.4, 22.1, 24.1, 26.0, 29.7, 30.9 and 34.1°. Furthermore, individual intensities show dependence on the type of molecule being encapsulated. For example, the 14.1 and 14.9 peaks resolve well in PS:thymol compared to PS:ibuprofen and PS:benzocaine; similarly integrated intensity of the 19.4° profile decreases from 8 to 7 to 5 (arbitrary units), respectively. These changes reflect the overall crystallinity, *e.g.* 22.5, 16.3, and 23.9% for PS:ibuprofen, PS:benzocaine and PS:thymol, respectively. Highest crystallinity of 27% was obtained after embedding sulfapyridine. Upon encapsulating benzocaine and curcumin, crystallinity increased by about 25 and 38%, respectively; but with ibuprofen, ascorbic acid and thymol, the increase is around 75%. A more than 100% increase is noticed after encasing sulfapyridine. Generally, in any powder diffraction, (1) appearance of new profiles, (2) shifts in existing peak positions or (3) variations in peak intensity, and in some cases all three, are due to re-organized atomic structure. In the present instance, observation of sharper peaks than in PS is a clear proof of complex formation. On the other hand, if it is just deposition or coating of guest molecules on starch granules then their diffraction should be noticeable, or else if the deposition is very little there should be no change in the starch diffraction pattern. The observed diffraction from each complex is not superposable on that from either component alone but is substantially modulated from that of starch. Thus, it can be inferred that the guest molecules are nested in the water channels of PS. Interestingly, the peaks at around 13 and 19° in the complexes are comparable to those observed in amylose–lipid complexes wherein amylose is in single helical conformation (Shogren, Fanta, & Felker, 2006; Tian et al., 2010). Diffraction pattern of PS with pure isopropanol (IPA) also show sharp peaks suggesting that the PS network loses its water when exposed to IPA as seen in the case of V-amylose (Buleon, Delage, Brisson, & Chanzy, 1990) and starch–alcohol complexes (Jane & Robyt, 1984).

The ability of water channels to capture guest molecules in starch network is further evidenced by unperturbed diffraction patterns of waxy maize (WS, A-starch) after complexing with ibuprofen and benzocaine (Fig. 2b). Interestingly, the diffraction is

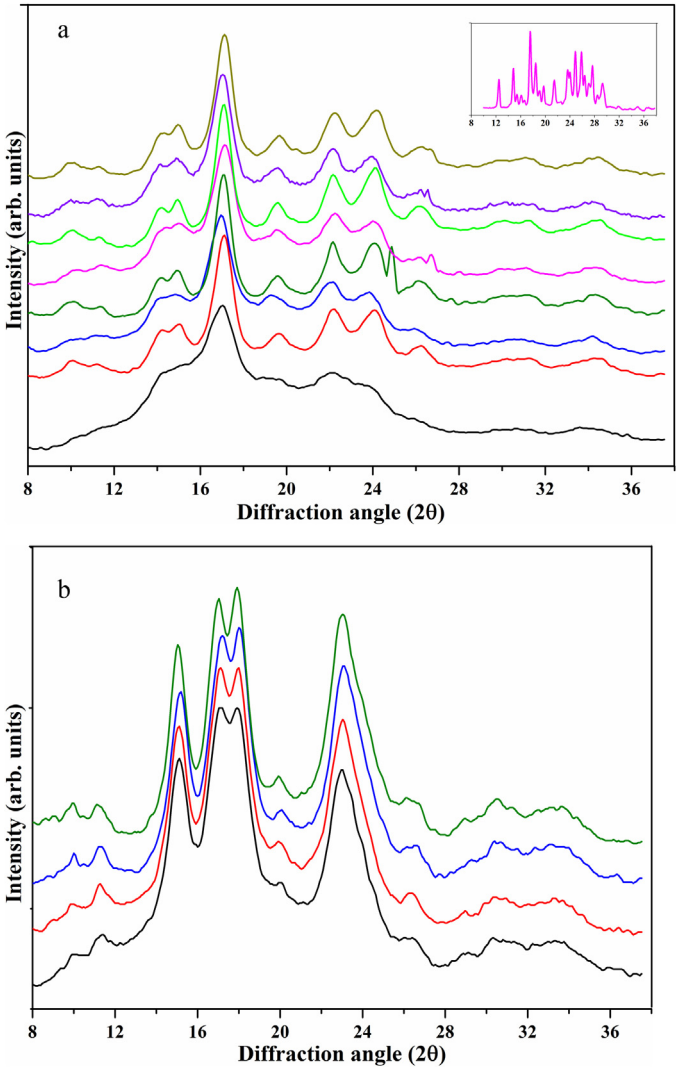


**Fig. 2.** (a) Comparison of X-ray powder diffraction patterns, in the diffraction angle range 8–38°, from potato starch (bottom) and its complexes with ibuprofen, benzocaine, sulfapyridine, curcumin, thymol, ascorbic acid and isopropanol (from second to top). In the complexes, development of well-defined profiles indicates the complex formation. Inset highlights the diffraction from curcumin. The other small molecules employed in this study also display similar sharp and crystalline peaks. (b) Comparison of X-ray powder diffraction patterns, in the diffraction angle 8–38°, from waxy maize starch and its complexes with ibuprofen, benzocaine and isopropanol (from bottom to top). The diffraction patterns of complexes are essentially the same and compare well with that of waxy maize starch.

more or less maintained by the added IPA but some increase in the relative intensities suggests the inherent role of IPA in removing amorphous water.

### 3.2. Spectroscopic characterization

Prominent changes in the FT-IR spectra are noticed in the 700–1900 $cm^{-1}$ region and Fig. 3 highlights the alterations in PS and WS after encapsulating the benzocaine and ibuprofen molecules. Qualitative analysis reveals that major absorption around 1000 $cm^{-1}$ occurs in PS and WS, however, in the complexes there are some extra bands that are present in neither PS nor small molecules. For example, in the case of benzocaine major peaks are observed at 769, 844, 1026, 1105, 1110, 1169, 1269, 1309, 1385, 1589, 1628, 1676 and 1736 $cm^{-1}$. Their position and intensity change drastically in the PS:benzocaine complex along with new peaks at 1203, 1216, 1228 $cm^{-1}$ suggesting favorable interactions

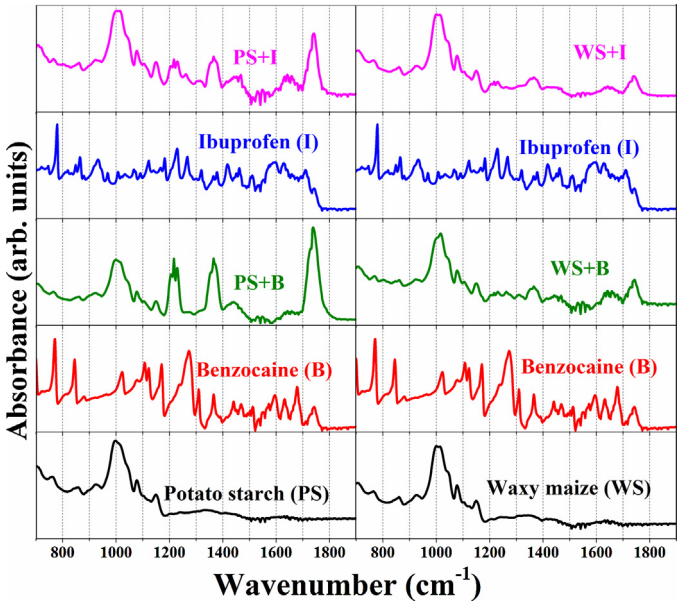


**Fig. 3.** Comparison of FT-IR spectra of potato starch (PS) and waxy maize starch (WS) and their complexes with benzocaine and ibuprofen in the spectral region of 700–1900 $cm^{-1}$. In case of PS complexes, either the peak shift and/or absence and/or appearance of new profiles indicate the starch:small molecule interactions, which are not present/prominent in WS complexes.

between the PS network and benzocaine molecules. Similar behavior is seen with ibuprofen and other complexes. On the other hand, the spectra from WS:benzocaine and WS:ibuprofen do not show much variations, and are more or less the same as the starting WS pattern with peaks overlaid from benzocaine or ibuprofen. Overall, FT-IR results in association with the X-ray observations are in support of the entrapment of guest molecules in the PS crystalline network.

### 3.3. Starch digestion

Instead of measuring digestion behavior of all the complexes, ibuprofen, benzocaine, and thymol complexes of PS have been chosen as representatives. Their *in vitro* digestion profiles are interesting. The percentage of starch digested during first 20 min is comparable with each other but major variations occur after 60 min. In native PS, the percentage of starch digested at 60 min is 12.7(7) but reduced to 7.5(7), 10.2(5) and 11.0(9) in PS:ibuprofen, PS:benzocaine and PS:thymol, respectively (Fig. 4). After 120 min, the values are 20.2(4), 15.7(1.7), 16.6(1), and 17.6(1), in the same order. Such changes concomitantly reflect in the RDS, SDS and RS amounts. All the samples maintain similar RDS amounts of 6.6% but SDS and RS quantities differ substantially. The individual SDS values for PS and its complexes with ibuprofen, benzocaine, and thymol are 13.1, 11.2, 9.9 and 11.3%, respectively, and RS contents are 79.9, 84.4, 83.5 and 82.4%. Overall, 24% decrease in SDS (for PS:benzocaine) and 6% increase in RS (for PS:ibuprofen) amounts attest to the ability of guest molecule encapsulation to modify digestion properties of uncooked PS.

## 4. Discussion

The research demonstrated in this communication is about adopting naturally available crystalline arrangement of starch and its water channels to encapsulate guest molecules while most of the earlier studies have relied on destabilizing the ordered starch network (Conde-Petit et al., 2006; Gidley & Bociek, 1988; Heinemann et al., 2001; Itthisoponkul et al., 2007; Le Bail et al., 2005; Nuessli

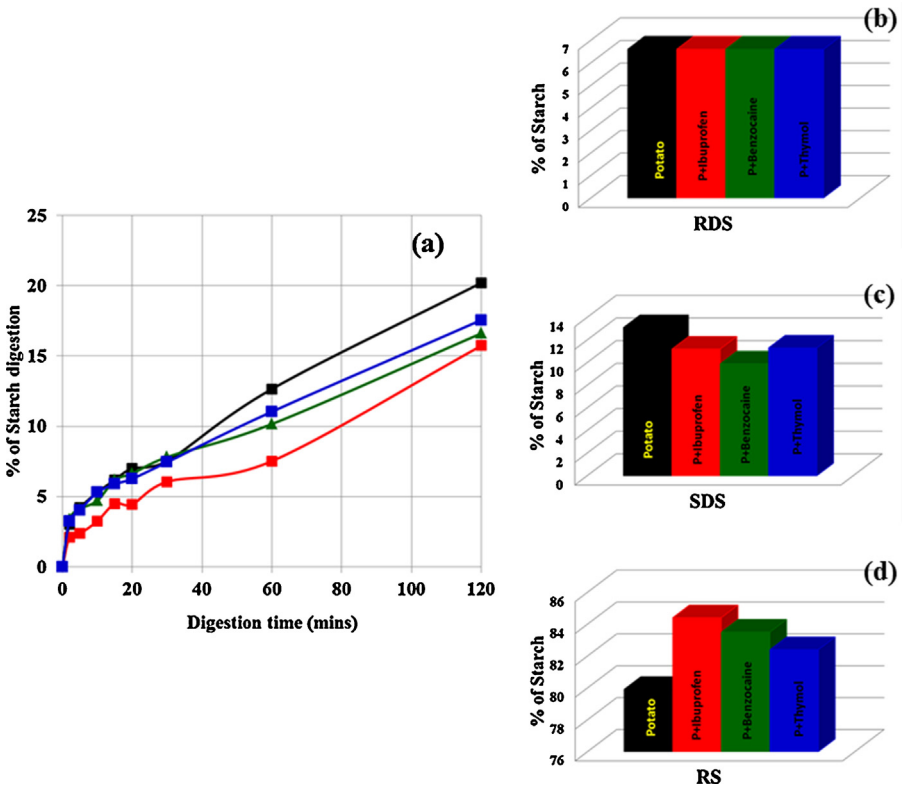


**Fig. 4.** (a) Starch digestion profiles of potato starch (uncooked) and its complexes with ibuprofen, benzocaine and thymol. Effect of encapsulated molecule on the % of digested starch is more pronounced at and above 60 min, and reflects well in the corresponding (b) RDS, (c) SDS and (d) RS values.

et al., 2003; Putaux et al., 2008; Rondeau-Mouro et al., 2004; Wulff et al., 2005). The novelty of this investigation is in exploiting the well-organized water channels unique to tuber starches. During biosynthesis, crystalline networks composed of ordered water molecules in channels are formed in B-starches. These channels are as wide as the starch double helix itself and this intrinsic feature can be exploited for entrapping guest molecules. The results from this study (Fig. 4) show favorable SDS and RS amounts of PS upon encapsulating guest molecules, suggesting yet another but an important approach in modifying starch digestion. The outcome should hold good for other B-starches such as cassava and high-amylose maize and C-starches such as pea and banana, as well as flours. The applicability of the proposed research does not limit to raw starches alone but should be equally valid to modified starches that are compatible with human digestive system. For example, physicochemical properties of starches can be modified through hydrothermal treatments (Gunaratne & Hoover, 2002; Jacobs & Delcour, 1998) without destroying the granule architecture, namely, by annealing and heat-moisture-treatment (HMT). Both these protocols involve starch storage at a certain moisture level, temperature and period of time, and modification occurs between the glass transition and gelatinization temperatures. Annealing does not perturb either the crystal structure or crystallinity of A- and B-starches but HMT transforms B- to C-type. Retrogradation and incubation at higher temperatures are another viable approaches for producing B-type networks (Shamai, Bianco-Peles, & Shimoni, 2003). This research could as well be extended to A-type but only after subjecting to enzyme, heat-moisture and acid treatments which yield both B- and V-type networks (Han et al., 2006; Hickman, Janaswamy, & Yao, 2009a, 2009b; Song, Janaswamy, & Yao, 2010). Overall, all these scenarios provide an array of elegant opportunities to encapsulate guest molecules, modify starch digestion and tailor glucose release in food products. Since isopropanol, used in this study to solubilize water insoluble molecules, is not compatible with humans, research with food grade organic solvents such as ethanol, acetone and propylene glycol will aid in reaping the complete advantage of the outlined research.

As RS does not undergo hydrolysis in the small intestine and is still available in the colon for fermentation, it is strongly believed that these results will be useful in developing targeted delivery of specific nutraceuticals or drugs for combating colon diseases and improving functionality. Further, the outcome has potential to serve as a basic commodity vehicle for developing food materials with SDS properties. The results clearly show that starch can be exploited to bind flavor compounds and thus alter the flavor quality of food products to the desired levels. In addition, a wide range of convenient and novel snack products can be endeavored with suitable amounts of nutraceuticals and vitamins that are ready-to-eat with little home preparation. A significant body of literature recommends the dietary intake of micronutrients especially vitamins for favorably reducing oxidative stress and inflammation (Palomer, Gonzalez-Clemente, Blanco-Vaca, & Mauricio, 2008; Shea, Ortiz, Nicolosi, Kumar, & Watterson, 2005; Webb, 2006; Zimmet et al., 2001). Recent reports accentuate that lack of vitamins C and E in regular diets could increase the risk of metabolic syndrome leading to T2DM and cardiovascular disease (Sempertegui et al., 2011). Development of foods rich in compounds that offer antioxidant mechanisms would be therefore beneficial; vitamins A, C and E, and several nutraceuticals are effective in this regard and this research will be highly favorable. Overall, the proposed methodology is elegant and novel for delivering nutraceuticals, drugs, vitamins and flavor compounds in food formulations using a GRAS material Starch with modulated digestion profiles.

## 5. Conclusions

World starch production in the year 2000, based on the estimates from European Union (EU) Commission and the United States Department of Agriculture (USDA), was 48.5 million tons (Holmes, 2005). Its demand has been increasing progressively for food and non-food applications: 66 million tons were used during the year 2008, with a projected 75 million tons by 2012 (Patil, 2012). The world-wide population growth coupled with surfeit dependence on convenient and processed foods continues to escalate the starch utility. Quoting Dr. Wilfred Oakley "Man may be the captain of his fate but he is also the victim of his blood sugar" (Oakley, 1962). Thus, modifying the digestion properties starch, the glycemic carbohydrate, and developing products with high SDS and RS proportions would indeed revolutionize starch utility in eradicating a number of health issues. Furthermore, exploitation of such heavily consumed staple material as a delivery vehicle of nutraceuticals, drugs and vitamins would be effective in developing health promoting and disease preventing foods. In order to realize the full potential of the proposed research, an in-depth study is necessary to develop food products with tailored digestion profiles for not only addressing T2DM concerns but also improving human health.

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