The comprehensive literature survey was carried out on hepatitis B infection, prevention and the vaccine development using HBsAg. The scientific knowledge as well as methodologies towards the designing of suitable oral delivery system can be used has been summarized below.

(Gallily, Vray et al. 1984) Studied the bacterial (Staphylococcus aureus H) uptake in macrophage cells was higher by 3.5 folds by means of Lectin WGA binding on bacterial surface. Binding of WGA with bacteria and macrophages was accomplished by -acetylchitotriose, a sacharide moiety that binds with WGA but not with monosachrides. Further soybean agglutinin and peanut agglutinin were also studied for macrophage uptake but not provides any improvement in the bacterial uptake due to they lack the ability to bind with bacteria while they are capable of to bind with macrophages.

(Iwanaga, Ono et al. 1999) prepared different liposomal formulations (PEG2000-Lip) and (Mucin-Lip) of using surface-coating with PEG 2000 and mucin and proves liposomal potentials towards oral delivery using insulin by protecting it from the proteases of the GIT secretions. Mean transit time of the PEG Lip was significantly more than both plain Lip and mucin-Lip that suggest the improved interaction of PEG-Lipo with mucus. Further higher hypoglycemic effects of PEG-Lip prove the more stability of Insulin inside the PEG-coated liposomes.

(Roy, Wu et al. 2000) delivered gold particles coated with DNA encoding HBsAg directly to the skin cells of human volunteers with one of 3 different doses 1, 2, and 4 µg. not any inflammatory sign were observed at the site of injection, plasma HBsAg specific antibody and CD4+ and CD8+ T cell proliferation as well as improved CTL responses were observed that proves the induction of Type 1 T helper cell immune response. (Luxembourg, Hannaman et al. 2006) delivers the electroporation based HBsAg specific DNA in normal mice and observed induction of multi specific CTL responses to HBV while it failed in the larger animals specifically in humans.

(Woo, Wong et al. 2001) designed a DNA vaccine by putting the necked DNA of HBsAg into live-attenuated Salmonella typhimurium. Mice were immunized via oral route and showed improved CTL responses than recombinant HBsAg Alum vaccine given subcutaneously. This strongly cellular vaccine (attenuated bacteria) make it better from the HBsAg Alum via effective delivery from mucus layer. (Maeng, Oh et al. 2001) demonstrated the circular dichroism (CD) studies of hepatitis B virus peptides and reported that viral capsid posses several important regions for virus neutralizing
epitopes and hepatocyte receptor binding sites. Affinity purified pre S1 segment of viral capsid consists of about 16% alpha-helical structure further it was demonstrated that this can form a secondary structure when binds with target site or in hydrophobic environment.

(Xing, Dawei et al. 2003) encapsulated liposomes in the calcium alginate beads for the oral delivery of bee venom peptide drug. Further observed the release behaviour of the peptide mimics the GIT condition and delivery system provides protection from the proteases of GIT. After oral administration to man γ-scintigraphy results proves that the formulated liposomes encapsulated system selectively targets the colon.

(Kakudo, Chaki et al. 2004) elucidated the membrane fusing behaviour of peptide receptor tagged bilayer structure of liposomes towards cells (Lipid bilayer membrane). This fusion was initiated by the receptor conjugated on the surface of liposomes and due to the similarity in the bilayer structure of liposomes and cell membrane these liposomes get fused and provides improved cell cytosol diffusion of Sulfo Rhodamine B. (Volodkin, Larionova et al. 2004) Formulated CaCO3 MPs with average diameter of 4.75 µm and used for peptide/protein (BSA, HRP) encapsulation using electrostatic layer-by-layer assembly technique. Peptide loading the CaCO3 MPs was affected by their diffusion rate affected by molecular weight. The process comprised of peptide encapsulation in porous network and followed by LBL deposition and core dissolution to form peptide encapsulated LBL capsule. Obtained results demonstrated that CaCO3 can be used for the synthesis of LBL polyelectrolyte coated capsules due to their properties to degrade at low pH. (Sukhorukov, Volodkin et al. 2004) Demonstrated preparation of porous CaCO3 microparticles of average size 5.0 µm and used as template for biomacromolecules encapsulation. Layer by layer deposition of oppositely charged polyelectrolytes was carried out to form LBL coated MPs. Core of LBL coated MPs was dissolved by means of acid treatment to get biomacromolecule encapsulated polyelectrolyte capsules. Obtained results established the adsorption of biomacromolecules in the pores of CaCO3 is affected by their electrostatic interactions with CaCO3 surfaces.

(Teillet, Dublet et al. 2005) studied mannose binding lectin assembled from homotrimeric structural units binds to neutral carbohydrates with higher binding capabilities and low dissociation (1:2) from glucose moieties than the monomeric form of lectin. (Zhang, Ping et al. 2006) synthesized lectin-modified SLNPs for oral administration of peptides (insulin) and proved the lectin conjugation with the SLNPs improves insulin
bioavailability in diabetic rat as well as improves protection of encapsulated insulin from the gastric and intestinal fluids when compared with non conjugated SLNPs. (Gao, Tao et al. 2006) formulated lectin conjugated PEG –PLA nanoparticles to target brain following nasal administration and observed about two fold increase in the brain deposition of coumerin loaded lectin-nanoparticles compared to plain nanoparticles. (Luxembourg, Hannaman et al. 2006) delivers the electroporation based HBsAg specific DNA in normal mice and observed induction of multi specific CTL responses to HBV while it failed in the larger animals specifically in humans. (Zhou, Bi et al. 2006) studied the molecular weight and size of recombinant HBsAg isolated from the Chinese hamster ovary and characterized by the high performance size exclusion chromatography and found the molecular weight of about 4921 kDa and size of about 22.1 nm in diameter. That supports the polymerization of 155 monomer HBsAg molecules to form a large peptide aggregate. (Yin, Chen et al. 2006) formulated PLGA nanoparticles by double emulsion method and Lectin WGA were attached covalently to the nanoparticle surface by applying carbodiimide chemistry. Release profile of encapsulated drug (Thymopentin) was evaluated for the change in the surface modification. Experiments with pig mucin suggested lectin WGA conjugated nanoparticles showed about 4 fold improved mucus interactions than plain nanoparticles. (Greenfield 2006) used Circular dichroism (CD) as a tool for determination of protein’s secondary structures and their proper folding in genetically engineered peptides expressed in the host cells. Shows the presence of negative peaks at 208 and 220nm is crucial for intact α-helical structure.

(Sarmento, Martins et al. 2007) developed solid lipid nanoparticles using solvent emulsification-evaporation method encapsulated with Insulin as a bio-molecule and characterized their efficacy towards oral administration. A considerable hypoglycaemic effect was observed by means of insulin loaded SLNPs in diabetic rats. That success fully demonstrated the improved intestinal absorption of insulin loaded SLNPs. (Gupta, Khatri et al. 2007) studied the transcytotic capabilities and expression of distinct carbohydrate receptors on the surface of intestinal M-cells and its application in the potential portal for the targeted oral vaccine delivery. They synthesized PLGA nanoparticles loaded with HBsAg and further surface of the nanoparticle was modified with Lectin WGA. Targeting of the surface engineered nanoparticles towards intestinal M cells was determined by applying Confocal Laser Scanning Microscopy (CLSM).
They conclude that HBsAg can be successfully stabilized by co-encapsulation of protein stabilizers. (Borges, Cordeiro-da-Silva et al. 2008) developed alginate coated chitosan nanoparticles of protecting the HBsAg, encapsulated in the chitosan nanoparticles while taking CpG oligodeoxynucleotide as an immune stimulant (adjuvant) and were given to mice via nasal route. Chitosan nanoparticle association sodium alginate encapsulating HBsAg gave rise to the humoral mucosal immune response. While humoral and systemic immune response were not induced by the HBsAg loaded chitosan nanoparticles alone. (Bharali, Pradhan et al. 2008) described the use of nanoparticles made up of methoxypolyethylene glycol–poly (lactide-co-glycolide) as a delivery system for HBsAg. Formulated nanoparticles were administered by the IM route to mice and the efficacy of the HBsAg-Nanoparticle was determined by measuring the serum IgG antibodies that shows higher serum IgG titer I in NP–HBsAg than free HBsAg. Improved uptake of fluorophore tagged nanoparticles was observed in bone marrow–derived dendritic cells applying CLSM. (Zhang, Miao et al. 2008) synthesized SLNPs for adefovir dipivoxil (ADV) and encapsulated with the octadecylamine-fluorescein isothiocyanate to study the uptake in the HEP G2 cells. Significantly improved inhibitory effects of ADV loaded in SLN on HBsAg, HBeAg and HBV genome was observed in the serum of infected persons while comparing to free ADV. (Chattopadhyay, Zastre et al. 2008) formulated SLNPs for the improve permeation of encapsulated atazanavir towards blood brain barrier using the in-vitro hCMEC/D3 cell line monolayer culture model. Observations have suggested the improved cell accumulation of atazanavir in cells it was also confirmed by using nanoparticle tagged with a fluorophore (Rhodamine 123). (Liu, Gong et al. 2008) developed SLNPs for pulmonary delivery of insulin through nasal administration and observed significantly increase in the insulin bioavailability in diabetic rats. Further fasting glucose levels were reduced to 39.41% after nasal administration of SLNPs-Insulin.

(Batista and Harwood 2009) Reported the role of B cells in generation of immune responses against immunogen. Article summarizes the mechanisms of antigen presentation by the APCs (macrophages dendritic cells) to B cells located in the secondary lymphoid tissues. Further they have described cell surface molecules those are important for the antigen presentation to B cells and B cells itself for antigen transport and presentation to T cells. (Nassimi, Schleh et al. 2009) Developed solid
lipid nanoparticles with varying lipid concentrations and evaluated their toxicity on lung cells (A549) in vitro and ex vivo on the lung slices isolated from healthy animal model (Rat). MTT assay as well as LDH release protocols were adopted for estimation of toxicity in the living cells. IC 50 values for SLNP were found to be 4080µg/ml and found that the developed nanoparticle system were safe for mucosal use due to higher observed IC 50 value. (Li, Zhao et al. 2009) developed quercetin loaded SLNPs of 155.3 nm size and evaluated their potential as the oral delivery system poorly water soluble drugs. Plasma concentration of the quercetin was monitored and they find out the QT-SLN showed about 571.4% increased oral bioavailability than quercetin suspension. (Salman, Irache et al. 2009) formulated mannose coated and Salmonella Enteritidis derived flagellin tagged bioadhesive poly anhydride nanoparticles encapsulated with ova. After the oral challenge of ova loaded surface modified nanoparticles both the formulations were shows higher serum IgG and mucosal sIgA titer in mice when compared to plain ova. (Werle and Takeuchi 2009) synthesized conjugate of polymer–protease inhibitor (chitosan–aprotinin) and encapsulated in between the positive and negative charged chitosan and lipid layers of multi layered vesicles (MLVs). CLSM imaging showed the significant difference in mucus penetration and adhesion properties of chitosan–aprotinin coated and chitosan coated MLVs. Further the MLVs with conjugated chitosan have increased blood circulation time in reference to chitosan coated MLVs. (Salmaso, Elvassore et al. 2009) formulated peptide loaded sub micron size solid lipid particles using gas-assisted melting atomization for controlled precipitation of lipids in supercritical carbon dioxide micronization. PEGylated SLNPs showed improved stability and better re-dispersion in water after lyophilisation than non PEGylated SLNPs further PEGylation improve the release behaviour and shows initial high release while non-modified SLNPs were showing more sustained release behaviour. Anti diabetic activity of Insulin encapsulated SLNPs showed the used method does not compromise with the insulin activity when given Sub-coetaneous injection. (Jain, Goyal et al. 2009) formulated PLA-PEG conjugated nanoparticles for the vaccination against hepatitis B for HBsAg for mucosal administration. Formulations prepared by both side conjugation of PEG in PLA (B-P-B) showed smaller particle size and encapsulation of HBsAg supported by high amount of PEG. B-P-B type nanoparticles showed improve humoral immunogenicity than compared with plain HBsAg, HBsAg-Alum and B-P type conjugated nanoparticles. (Mukherjee, Ray et al. 2009) Highlighted the importance and
applications of the solid lipid nanoparticles in drug delivery. SLNP shows their potential for broad range of drug molecules with variable size and zeta potential distribution. Due to their scalability, low cast production and small size and size distribution makes them useful for secondary and treachery levels of drug targeting strategies.

(Liu, Yang et al. 2010) used HBsAg as the target receptor for the HBV infected cells HBsAg is synthesized in the infected cells and their affinity towards lipid molecules assembles HBsAg molecules on the surface of infected cell. They have used RNA aptamer (HBs-A22) specifically designed to capture HBsAg molecules and targeting efficiency was checked towards the HepG2.15 that expresses HBsAg but did not bind to HBsAg-devoid HepG2 cells. (Greiner, Egelé et al. 2010) characterized the polymeric behaviour of HBsAg molecules using Fluorescence correlation spectroscopy experiments suggest the presence of low emissive Trp embedded and high emissive Trp at the surface of HBsAg particles. On the basis of their findings they have proposed a structural model for S proteins in HBsAg which showed reduced flexibility that is due to their higher interaction towards lipids and deeply penetrated in the lipid core. (Mishra, Mishra et al. 2010) formulated SLNPs using solvent injection method with HBsAg and studied the surface modifications with mannosylation to improved cellular uptake in macrophages and dendritic cells. In-vivo immunogenic responses showed significantly higher in HBsAg-SLNPs (Mann) formulation in comparison to plain HBsAg and non-targeted HBsAg-SLNPs after subcutaneous administration to mice. (Muttil, Prego et al. 2010) formulated nanoparticle-aggregate containing Hepatitis B surface antigen (HBsAg) were prepaid by using (PLGA)/polyethylene glycol as an polymeric excipients and administered to the lungs of guinea pigs. Antibodies titers of the HBsAg were evaluated in serum as well as the at mucosal secretions showed the inhaled HBsAg nanoparticle formulation is capable of generating high amount of HBsAg specific serum IgG and levels of sIgA were also found in the mucosal surfaces of Lungs as well as at the vaginal and intestinal mucosal secretions. (Wood, Stone et al. 2010) formulated pH responsive hydrogels complexation composed of methacrylic acid and functionalized poly (ethylene glycol) tethers conjugated with the lectin WGA were studied for oral delivery of peptides (insulin). In caco2 cell cultures Lectin WGA improves insulin permeability by 9 fold as compared to insulin solution. Further results were validated on the HT 29 cells and caco2 cell co culture as mucus secreting cell
monolayer and observe about 5 fold increase in insulin transport in lectin WGA conjugated than plain insulin.

(Nassimi, Schleh et al. 2010) evaluated the cytotoxic behaviour of formulated SLNPs on A549 using MTT assay. However after 16-day of repeated-dose, inflammatory effects were estimated by quantitation of total protein content, LDH, chemokine KC, IL-6 in the respiratory tract and showed the delivery system was not toxic up to 16 days of regular dosing. (Bhowmick, Mazumdar et al. 2010) studied Ag encapsulation and cell uptake of liposomes prepared by applying different methods like multilamellar vesicles (MLV), dehydration–rehydration vesicles (DRV) and reverse-phase evaporation vesicles (REV). Antigen (Leishmania donovani promastigote membrane antigens) encapsulate in liposomal formulations were immunized to the mice (IM route) and challenged them for the pathogen after 10 days of vaccination. Observations suggests that the Ag encapsulated in the MLVs were more resistant towards pathogen challenge that attributed by the sustain release behaviour of Ag from MLVs.

(Saini, Jain et al. 2011) developed single-shot HBSAg loaded PLGA microspheres and explored their capability to stimulate cell mediated immune responses. HBSAg loaded PLGA MPs were given via sub coetaneous injection to mice and observed significantly higher IFN-γ, IL-2 and nitric-oxide than marketed HBSAg vaccine. (Mishra, Tiwari et al. 2011) presented a study targeted at exploring the efficacy of α-l-fucose specific, LTA (Lotus tetragonolobus from Winged or Asparagus pea) as a nanoparticle targeting device to target the intestinal M cell to evoke effective immune response against encapsulated HBSAg. They synthesized LTA grafted poly(lactic-co-glycolic acids) (PLGA) nanoparticles with HBSAg in the core of the nanoparticle. Specific uptake of nanoparticle by peyer's patch was investigated by applying confocal laser scanning microscopy (CLSM). The induction of immunological reactions and their potential were assessed by measuring anti-HBSAg titer in serum of mice model (Balb/C), while induction of the mucosal immunity was analyzed by estimating secretory immunoglobulin A (sIgA) level in the salivary, intestinal, and vaginal secretion.

(Demento, Cui et al. 2012) formulated liposomes and PLGA nanoparticles and compared them towards the efficacy of each delivery system in a long-term immunization study resulted in protection against a model bacterial pathogen. Ag loaded nanoparticles were elicited prolonged antibody titers compared to liposomes and alum both further extent of the cellular immune response was also highest in mice vaccinated with Ag loaded Nanoparticles these findings suggests the after IM dosing
Liposomes were not able to survive for the prolonged time period while PLGA nanoparticles perform slow Ag release and persist for long time. (Kumar, Gupta et al. 2012) and (Gupta, Kumar et al. 2013) prepared layer by layer coated CaCO3 microparticles for effective delivery of flavonoid (Kempferol). Developed delivery system changes their characteristics after passing through gastric conditions due to reduced pH mediates CaCO3 core dissolution and formation of ultrathin layer by layer coated nanocapsules. Significant difference in the Osteoprotective and bone regeneration effects were observed after oral administration of KEM loaded LBL nanocapsules than plain KEM.

(Subbiah, Ramalingam et al. 2012) formulated N,N,N-trimethyl chitosan nanoparticles encapsulated with HBsAg provides long lasting HBsAg release for up to 43 days. Formulated nanoparticles were given via nasal administration in Balb/C mice and proved the hypothesis of adjuvant effect of nanoparticle by determining the serum IgG titers. Obtained finding showed that N-TMC NPs could be extensively used in intra nasal delivery of therapeutic protein and antigens. (Joshi, Patel et al. 2012) formulated SLNPs encapsulated with ondansetron HCl (OND) for intranasal delivery and analyzed the function of different lipid and surfactant ratios for their size and zeta potential distribution using factorial design as a mathematical tool. After intra nasal administration SLNPs accumulation in the brain was characterized by applying Gamma scintigraphic imaging. (Yu, Kim et al. 2012) formulated cationic SLNPs for co-delivery of paclitaxel and siRNA and observed improved transfection efficiency of SLNPs in KB cells using fluorescence-labeled dsRNA. Further MCL1 mRNA levels were found significantly less in KB cells treated with SLNPs, while the expression was not halted in plain siRNA (siMCL) alone.

(Carrillo, Sánchez-Hernández et al. 2013) synthesized positively charged SLNPs as a simultaneous delivery of drug and nucleic acid (siRNA). Nanoparticles were of 340nm size with +44 zeta potential showed improved siRNA loading and transfection efficiency. (Lugade, Bharali et al. 2013) formulated HBsAg loaded chitosan nanoparticles and compared its immunogenicity with free HBsAg and HBsAg with Alum. In vivo findings in Balb/C mice after intra muscular administration showed significantly higher serum IgG titer in case of nanoparticle encapsulated HBsAg than HBsAg with alum. (Lason, Sikora et al. 2013) formulated nanostructed Lipid carrier system to optimize the process parameters and surfactants on their size and drug loading. Optimized SLNP formulations were of size range between 60 to 80 nm, and
zeta potential was about -30mV were found stable that was further confirmed by macroscopic observation using SEM and TEM. (Wilson, Keller et al. 2013) investigate the use of pH-responsive, endosomolytic polymer nanoparticles developed for RNA with peptide delivery vehicle for vaccination. Diablock polymer composed of an ampholytic core-forming block and a redesigned polycationic surface with an average size of 23nm and encapsulated with CpG ODN and a thiolated protein antigen. Subcutaneous injection of Ag-nanoparticles stimulated significantly higher immune response than free Ag and Physical mixture of Ag and CpG ODN. Further a dual-delivery carrier significantly improves CD4+IFN-γ+ production and elicited a balanced IgG1/IgG2c antibody response. (Delgado, del Pozo-Rodríguez et al. 2013) encapsulated 3 different gene sequences that differs in their molecular weights to SLNPs formulation and observed high rate of transfection in HEK-293 cells. Further intravenous administered SLNPS were able to induce expression of EGFP in the spleen, lung and liver of mice and proves the potential of SLNPs in gene delivery. (Yuan, Chen et al. 2013) Studied the potential of PEGylated lipid nanoparticle system (SLNPs) for mucosal delivery purposes. For effective mucosal delivery mucus penetration behaviour of the formulated nanoparticle was evaluated in depth on the mucus secreting cells (Caco2 cell and HT 29 cells) as well as ex vivo mucus slab (pig mucus). Cell uptake results on the caco2 cells suggests deceased uptake of PSLNPs than plain SLNPs and in the mucus secreting co-culture of HT 29 cells with caco2 cells suggested higher uptake of pSLNPs than SLNPs this confirms the mucus penetration behaviour of the nanoparticles significantly alters the cell uptake in mucus secreting system. (Nafee, Husari et al. 2014) formulated SLNPs using positively charged lipids and efficiently delivered gene sequences of QS inhibitor to the cystic fibrosis in the respiratory track. Findings reported that the lipophilic nature of the formulated SLNPs helps in the cell membrane interactions to facilitate the optimum transfection efficiency of loaded gene sequence. Further QS inhibitor loaded SLNPs formulation showed up to 7 fold improved anti-virulence efficacy while observations reported plain SLNPs also exhibited some extent of anti-virulence properties.(Fan, Chen et al. 2014) developed ligand modified SLNPs to improve oral bioavailability of peptide drug evaluating the influence of mucus on peptide bioavailability. CSK and IRQ peptides were used as the two surface ligands and conjugated with SLNPs loaded with salmon calcitonin. CSK and IRQ modified SLNs showed better drug protection ability compared with unmodified SLNPs and facilitate the peptide transport through caco2 cell monolayer
and in-vivo studies proves SLNPs feasibility towards oral peptide delivery. (Li, Sun et al. 2014) Formulated LBL coated mesoporous silica nanoparticles loaded with Doxorubicin for effective delivery in cancer cells. Further obtained results of in vitro release profile from LBL coated silica nanoparticles showed several fold reduced release of encapsulated DOX than plain silica nanoparticles. In vitro cell uptake results suggests site specific release of encapsulated DOX (endosomal pH) in case of LBL coated silica nanoparticles that was attributed by the layer crosslinking at different pH conditions that supports higher release of encapsulated molecules at acidic pH.

(Christophersen, Birch et al. 2015) observed the Lysozyme distribution patterns in the core of solid lipid microparticles formulated with various lipid compositions using coherent anti-Stokes Raman scattering method. observations were further confirmed by the release behaviour of lysozyme from SLMPs that confirms the solid content of used peptide goes inside the core of the MP and so provides sustained release while formulations made by the aqueous solution of Lysozyme shows initial burst release. (Su, Yi et al. 2015) formulated HBsAg conjugate with Truncated PD peptide (a non antigenic peptide expressed in the E coli) with the help of glutaraldehyde. Intra muscular injection of conjugated HBsAg provides significant improved plasma IgG titers than dissolved HBsAg. Moreover conjugated vaccine showed improved Th1 immune responses, as well as Th2 responses were also activated and induces antibody production. (Liu, Zhang et al. 2015) Studied behaviour of mucus in protection of mucosal tissues and its role in elimination of foreign particles from adsorbed mucus layer. Article focuses on the describing nanoparticles mucopenetrating and mucoadhesive properties and strategise to investigate nanoparticle interactions with mucus layer. (Farhadian, Dounighi et al. 2015) Prepared nanoparticle delivery system for oral vaccination using trimethyl chitosan (TMC). Obtained results suggest peptide degradation by means of proteolytic enzymes in GIT and to overcome these harass proteolytic degradation peptide encapsulation in nanoparticle matrix is the option for effective oral delivery of peptide vaccines (HBsAg). (Wang, Zhen et al. 2015) formulated a liposomal formulation MLLs encapsulated with HBsAg induces robust systemic immunogenicity as high levels of HBsAg-specific IgG were detected in serum and induces mucosal immune responses sIgA in the salivary, vaginal and intestinal secretions.

(Das and Bhaumik 2016) Demonstrated the influence of layer by layer coatings on surface roughness with different LBL coating thickness. Observations suggest that the
coatings on the surfaces significantly reduces surface roughness form (Ra = 0.0899 µm) of bare surface to (0.0338 - 0.289 µm) in case of coated surfaces. (Hurley, Pirzai et al. 2016) Prepared a monolayer of intestinal epithelial cell (Caco-2, T84, and HCT-8) on permeable Transwell™ filters and evaluated the reduction in TEER by applying different class of peptide and proteins on the cell monolayer. Results suggested that this model system can effectively distinguish between the hazardous and nonhazardous proteins for the oral administration.