Review of literature
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Hepatitis - Immunization Programme

Globally, HBV is a major cause of acute and chronic hepatitis. Chronically infected patients are suffering from complications ranging from liver functional abnormalities to life threatening hepatocellular carcinoma. Vaccine preventable hepatitis is a term used to describe infection with HAV, HBV or both. The lengthy history of efforts to describe, delineate, control and prevent hepatitis A and B is noteworthy for many scientific achievements. Efforts to prevent and control hepatitis A and B have posed enormous problems to public health and health care delivery systems. Great advances in control of HAV and HBV infections occurred following the availability of vaccines to induce active immunity. The incidence of hepatitis activation and hepatocellular carcinogenesis was elucidated in patients with HBeAg and normal aminotransferase by Kenj ikeda et al, (2006). The study was performed for long term in retrospective cohort. They have concluded that advanced stages of hepatitis were some times found in HBeAg negative and aminotransferase normal HBV carriers. Jody Hershey et al, (2005) stated that the hepatitis A and B vaccinations should be integrated in to public health settings that serve adults at high risk for infections and a policy of Universal immunization may be the best way to accomplish this goal of these settings. Even though hepatitis vaccines should be given to all susceptible people at high risk, many opportunities to vaccinate adults at high risk are missed, and there are several barriers and challenges to vaccinate the adults. Recommendations to make hepatitis vaccination in adult’s routine practice will assist public health efforts to prevent diseases by communicating the importance to both medical providers and policy makers. A number of obstacles can interfere with
appropriate and timely hepatitis immunization. The basic difficulty is the very high cost of hepatitis A and B vaccines and is out of reach for many uninsured patients. However, many private and government sponsored insurance programmes do not routinely cover these vaccinations for patients with chronic liver diseases. The effect of American government and national organizations such as Centre for Disease Control and Prevention (CDC) and American Association for the Study of Liver diseases (AASLD), may lead to uncertainty and inconsistent vaccination practices. This situation is mainly due to multiple office visits for prescreening assessment and vaccine administration. Kathleen et al, (2005) suggested that the combination of interventions could be used to facilitate timely and appropriate vaccination against hepatitis and to improve the affordability of vaccination for patients with chronic liver diseases. The current paediatric vaccination schedules in the United States are based on age. In contrast adults are vaccinated against most infectious diseases including hepatitis A and B when they are identified as at high risk or after a known exposure. There are multiple risk factors for hepatitis A and B of which clinicians often are not aware. Consequently, many persons at high risk are never vaccinated. Universal vaccination against hepatitis A and B is recommended for adults to combat transmission of virus and prevent long term sequel. Stanley Gall, (2005) suggested that all older adolescents and adults should be vaccinated regardless of risk factors and greater efforts should be made to educate physician about the need to vaccinate their patients against hepatitis. Young et al, (2003) evaluated the long term efficacy of childhood hepatitis B vaccination programme. A total of 1112 new born babies of hepatitis B carrier mothers were given HBIG and a 10 μg three doses regimen of plasma derived vaccine administered at a conventional (0, 1, 6 months), delayed (2, 3, 8 months) or accelerated (0, 1, 2 months) schedule. The vaccines were followed to
determine their anti-HBs status over a 16-year period. Upon completion of the vaccination schedules, 92.6% developed antibody against surface antigen (anti-HBs) seroconversion, the rate of which fell to 33.3% at year 16. The three schedules were equally effective in preventing chronic infection, with a protective efficacy of 88.9% from hepatitis B surface antigen (HBsAg) carriage, compared with historical control. Vaccinees on the delayed schedule had a slightly higher seroconversion rate over years, and were better able to maintain an anti-HBs level of $\geq 100$ IU/L. Overall, a quarter demonstrated evidence of exposure to the virus, being positive for antibody against core antigen or HBsAg, or mounting a rise in anti-HBs during the follow-up period. They concluded that a three-dose hepatitis B vaccine regime is generally effective in protecting newborns of hepatitis B carrier mothers from infection and chronic carriage. Booster was not needed even after 16 years of monitoring. David Fitzsimons et al. (2003) noted the utility of new combined hepatitis B vaccines. The status and likely impact of existing and potential new combined hepatitis B vaccines were broadly considered at the Viral Hepatitis Prevention Board (VHPB) meeting in Malta in October, 2001. In that meeting, the currently available and/or licensed combined hepatitis B vaccines in Europe and the prospects for further such vaccines were reviewed. The information exchanged testified further to the fact that combined vaccines containing a hepatitis B component are safe, effective, licensed, available, and used. But they are not yet cheap. The authors stated the impact of availability of combined hepatitis B vaccine on hepatitis B immunization programmes in Europe.

The effectiveness in the prevention of perinatally transmitted HBV infection was assessed by Tommaso Stroffolini et al. (2003) in 11858 pregnant women consecutively recruited in public and private hospitals in six Italian regions during 2 months period in 2001. Out of them 10881 pregnant women attended HBsAg
antenatal screening. The overall HBs Ag prevalence was 1.7% and it was 1.4% in pregnant women born in Italy but 5.9% in those born in Asia, Africa, Central and South America, and Eastern Europe. The findings demonstrated that antenatal screening showed good effectiveness in the prevention of perinatal transmitted HBV in Italy. Hashem B. El-Serag (2002) reported that chronic infection with hepatitis C virus could be a major risk factor for the development of hepatocellular carcinoma (HCC). However, factors that predispose to HCC among HCV infected person included male sex, older age, hepatitis B virus co-infection, heavy alcohol intake, diabetes and transfusion related source of HCV infection. The livelihood of development of HCC among HCV infected persons was difficult to determine because of paucity of adequate long term cohort studies. The antiviral therapy of patients with HCV related cirrhosis might reduce the further risk of HCC. During the past 25 years the mortality caused by HCC has doubled in the United States. The prevalence rate of HCC would become double in United States in the next 10-20 years. Therefore, they suggested that future research must focus on improving understanding of the incidence and risk factors for HCC, causes of HCV related carcinogenesis, means of early detection and better treatment for HCC. The efficacy of combined vaccines in pediatric vaccine delivery was demonstrated by Supamit Chunsuttiwat et al., (2002). The study demonstrated the performance and cost implications for the use of combined DTP - HB vaccine in the Thai immunization programme. In the study, separate DTP and HB vaccine and combined DTP – HB vaccines were used in the infant immunization programme in Chiangrai Province during a 4 year period. The study was unable to demonstrate that the combined DTP – HB vaccine was more economical than the separate DTP and HB vaccine. Tak Mao Chan et al., (2002) demonstrated the impact of lamivudine treatment on patient
survival, the optimal time to start treatment and the feasibility of discontinuing treatment. In this research work, serum hepatitis B virus (HBV) DNA levels were measured serially in HBsAg positive kidney transplant recipients, and lamivudine was administered preemptively to patients with increasing HBV DNA levels with or without elevations of aminotransferase levels. The treatment criteria were met by \textit{de novo} patients at $8.4 \pm 6.2$ months after transplantation. Suppression of HBV DNA and normalization of aminotransferase levels were achieved in all treated patients and 21.4% had HBcAg antigen seroconversion. The survival of preemptively managed \textit{de novo} transplant patients was similar to that of HBsAg negative controls. Among all, eleven patients developed lamivudine resistance. Moreover, discontinuation of lamivudine was attempted in 12 low-risk patients after stabilization and was successful in 5 patients. They concluded that preemptive lamivudine therapy based on serial HBV DNA levels and clinical monitoring improved the survival of HBsAg positive renal allograft recipients. The Lamivudine treatment could be discontinued safely in selected patients after stabilization to minimize the selection of drug resistant HBV mutants. Risbud \textit{et al} (2002) estimated the prevalence and incidence of hepatitis B virus infection among patients, attending three STD clinics in Pune, India. Out of 497 patients 3.6%, 26.5% and 43.2% were positive for HBsAg, anti HBs and anti Hbc respectively. Moreover, tattooing was found to be independently associated with presence of core antibody. A high prevalence and incidence of HBV infection was observed in STD clinic attendees and stated the need of hepatitis B vaccination to commercial sex workers and their clients in India. The current methods of detecting hepatitis B virus mutations are time consuming, labor intensive and not suitable for screening large number of samples (Manna Zhng \textit{et al}, 2002). They documented the advantages of a system that exploited differences in thermal stability between perfect
match and mismatch hybrids and thereby distinguished between wild type and mutants. They designed hybridization probe complementary to specific wild type HBV sequences in surfaces, precore and basal core promoter region of HBV genome. The genomic sequences of mutant and wild type viruses were confirmed by direct sequencing. Real time polymerase chain reaction with fluorescent hybridization probes accurately identified each mutant and wild type genome. They concluded that real time PCR with fluorescent hybridization probes is a specific, sensitive, quantitative and rapid means of detecting clinically relevant HBV mutants.

Sulkowski et al, (2002) stated that the use of HIV – 1 specific non nucleoside reverse transcriptase inhibitors such as nevirapine (NVP) and efavirenz (EFV) caused severe hepatic injury. They studied the incidence of severe hepato toxicity among 568 patients receiving non nucleoside reverse transcriptase inhibitors (NNRTI), among whom, 312 and 256 patients were prescribed EFV and NVP respectively. They observed that severe hepato toxicity was noted in 15.6 % of patients prescribed with NVP and 8% of those patients prescribed with EFV. Margaret Burgess et al, (2001) reported an open study on the reactogenicity and safety of two dosing schedules (0,6 or 0, 12 month) of an adult formulation of combined hepatitis A and hepatitis B vaccine containing 720 ELU of inactivated hepatitis A antigen and 20 µg of hepatitis B surface antigen in healthy volunteers aged 12 – 15 yrs. The vaccine was well tolerated and reactogenicity of both vaccination schedules was equivalent. The results thus demonstrated that the combined hepatitis A and B vaccine could be administered using flexible vaccination intervals, which made it suitable for use in large scale hepatitis immunization programmes.
Microencapsulation techniques

Polymer microspheres have shown great potential as a next generation adjuvant to replace or complement existing aluminium salts for vaccine potentiation. Microsphere-based systems can now be made to deliver subunit protein and peptide antigens in their native form and in a continuous or pulsatile fashion for periods of weeks to months with reliable and reproducible kinetics, often obviating the need for booster immunizations in animal models. In recent years great effort has been made to improve the efficacy of vaccination by using novel adjuvants or antigen delivery systems. Controlled release of antigens from polymer microparticles has been of particular interest to those interested in the development of vaccines which could be effective in a single dose i.e single-step immunization.

Waree Tiyaboonchai and Nanteetip Limpeanchob (2007) fabricated a new nanoparticulate delivery system for amphotericin B. In their work, two opposite charged polymers were used to form nanoparticles through electrostatic interaction, chitosan a positively charged particle and dextran sulfate a negatively charged polymer linked together and hardened by Zinc sulfate. Li Feng et al (2006) investigated that the feasibility of a single-dose hepatitis B vaccine based on three kinds of poly (D, L-lactide-co-glicolic acid) (PLGA) microspheres. PLGA microspheres loaded with recombinant hepatitis B surface antigen (HBsAg) were formulated using a double emulsion microencapsulation technique. The pharmaceutical characteristics of size, surface morphology, protein loading efficiency, antigen integrity, release of HBsAg-loaded PLGA microspheres and degradation of the polymer in vitro were evaluated. The degradation of the polymer corresponded with the composition of the polymer (lactide / glycolide ratio), molecular weight of the polymer (viscosity) and morphology of the microspheres. These PLGA
microspheres were able to continuously release antigen under conditions that mimic the environment in vivo. The single subcutaneous injection of HBsAg-loaded PLGA 50 / 50 microspheres, PLGA 75 / 25 microspheres and a mixture of PLGA 50/ 50, PLGA 75 / 25, and PLGA 50 / 50-COOH microspheres in mice resulted in comparable serum antibody titers to those of three injections of the conventional aluminum adjuvant formulated HBsAg vaccine. Based on these findings in vitro and in vivo, it was concluded that HBsAg was successfully loaded into the PLGA microspheres, which can auto-boost an immune response, and the HBsAg-loaded PLGA microsphere is a promising candidate for the controlled delivery of a vaccine.

Gavini et al (2006) stated the loading of carbamazepine in to the polymeric carriers always led to an increase in the dissolution rate compared to carbamazepine raw material. They concluded that the microspheres obtained using chitosan glutamate had the best behaviour both in vitro and in vivo. They increased the drug concentration in the serum when compared to the nasal administration of the pure drug. Sunil Agnihotri and Tejraj Aminabhavi (2006) demonstrated a novel interpenetrating network chitosan – poly (ethylene oxide – g- acrylamide) hydrogel microspheres for the controlled release of capecitabine, an anticancer drug by emulsion cross linking method using glutaraldehyde as cross linker. The dextran derived biomaterials have been considered to compatible matrices for protein and bioactive drugs because of their hydrophilic properties and ability to control drug dissolution and permeability (Fa - ming chen et al, 2006). A novel class of dextran – glycidylmethacrylate (Dex –GMA) / Poly (ethylene glycol) (PEG) microspheres were designed and synthesized by polymerization of DEX- GMA emulsified in an aqueous PEG solution. The drug loading and in vitro drug release was evaluated by routine procedure and the biological activity of BMP loaded microspheres was studied by
experimental cytology methods. Cytology studies showed rh BMP-2 microspheres have good biological effects on cultured periodontal ligament cells and could achieve a long action time than concentration of rh BMP-2 solutions.

The importance of developing new vaccine systems with proper attention to develop controlled delivery system was demonstrated by Stanley Davis et al. (2006). They stated polymer microspheres and lamellar particle based on the biodegradable materials PLA and PLGA could be employed for the improved parenteral and mucosal administration of antigens. Like wise soluble biopolymers such as chitosan could be used for the nasal delivery of various antigens as well as DNA. The process of optimization is one of the most important biological barriers to controlled drug delivery (Donald Owens et al, 2006). Sangmook Lee and Jae Wook Lee (2005) investigated the thermal, rheological, morphological and mechanical properties of a binary blend of poly (lactic acid) and poly (butylenes succinate adipate). Young Hong et al (2005) investigated the physical stability of spray dried proteins with surfactant free hydro fluro alkane pressaurised metered dose inhalers during prolonged storage. The results indicated that the presence of PVA in the spray dried stabilized protein particles could enhance the physical stability of microparticles. Derek O’ Hagan et al (2004) evaluated that the ability of naked DNA encoding intracellular forms of E1 & E2 envelop proteins from HCV to induce antibody responses and compared the responses induced with same plasmid adsorbed on to cationic poly (lactide – co – glycolide ) micro particles. The results showed that cationic PLG micro particles with adsorbed HCV DNA generate potent immune responses. Shyh Ming Kuo et al (2004) demonstrated a one step method for fabricating chitosan microspheres. The fabricated by simple and in situ method by using high electrostatic system. The chitosan microspheres exhibited good sphericity and smooth morphology. They have stated
that the size of the microspheres was decreased when the electrostatic field strength was increased.

Freiberg & Zhu (2004) stated that polymeric microspheres could be employed to deliver medication and the vaccine was released from a microsphere by leaching of polymer or by degradation of the polymer matrix. Since the rate of drug release was controlled by above two factors, the understanding of the physico chemical properties of the releasing medium was found to be important. Thus, the authors discussed the physico - chemical properties that affected the formation, structure and sphere size. Radi Hejaji and Mansoor Amiji (2003) reviewed that chitosan is a natural polymer obtained by alkaline deacetylation of chitin, is non toxic, biocompatible and biodegradable. They have stated that these properties made chitosan as a good candidate for the conventional, novel gastro intestinal drug and gene delivery systems. The ability of chitosan to enhance both the systemic and local immune responses against diphtheria toxoid after oral and nasal administration was demonstrated by Inez Vander Lubben et al, (2003). DT associated to chitosan microparticles resulted in systemic humoral immune responses and local immune response against DT after oral vaccination and in significant enhancement of IgG production after nasal administration. Hence the experiments demonstrated that chitosan microparticles were very promising mucosal delivery system. Regine Audran et al, (2003) showed the biodegradable microspheres consisting of poly (D, L- Lactide – co- Glycolide) as a promising alternative to conventional adjuvants. The adjustable pulsatile release of encapsulated material from microspheres made mimics the priming and boosting injections of conventional immunization regimens. They demonstrated that microspheres could serve as antigen reservoirs in antigen presenting cells, so that antigen is presented for extended periods up to 9 days. The
results clearly indicated the paramount importance in cancer vaccination therapy since microspheres might serve as antigen reservoirs to extend the presentation by APC used to boost the patient's immune response to tumor antigen. The controlled release microspheres could overcome many of the disadvantages of multiple vaccine delivery such as rate of uptake and cost of administered proteins and peptides were difficult to administer using conventional polymers owing to protein degradation, premature release and stability (Jennifer Moynihan et al, 2002). However, they developed stable microspheres at room temperature by formulating using oligosaccharide ester derivatives (OEDs) of trehalose and synthetic peptide analogue of hepatitis B surface antigen. The microspheres developed strong immune responses without the requirement of multiple doses or cold chain storage and radically improved immunization programme in developing countries.

Diwan et al, (2001) reported that the biological activity got compromised when encapsulated in controlled release of microspheres during formulation. In their study, preformed microspheres made up of cross linked dextran were employed as a matrix for conjugation of tetanus toxoid under aqueous conditions. The native immunoreactivity of TT was completely retained after conjugation and confirmed by immunofluorescence and quantitative ELISA. Immunogenicity of Dex TT conjugative was tested in rodents. No untoward mortality or adverse effects of immunization with test material was observed on histopathology of the site of injection. A single immunization with the long lasting depot formulation elicited anti TT antibody response was observed for 1 year with out any need of booster. The relationship between the volume of liquid installed in to the nasal passages and the development of immunological response was studied by Jim Eyles et al, (1999). Groups of six mice were intra nasally immunized with soluble or micro encapsulated
tetanus toxoid on pre determined days 1, 4 and 28 of the study. Microspheres suspensions and tetanus toxoid solutions were nasally instilled in two different volume of buffer (10 or 50 μl). Nasal installation of microspheres in 10 μl of buffer generated statistically depressed (P < 0.001) tertiary serum anti toxoid Ig G responses in comparison to animals immunized with 10 or 50 μl, which of soluble or 50 μl generated stastically (P < 0.005) superior levels of specific IgG and IgA antibodies in day 49 lung wash samples.

Maria Alonso et al, (1999) developed a single dose tetanus vaccine based on poly (lactic acid) PLA or Poly (Lactide-co-Glycolide) microspheres, which became complicated due to the instability of tetanus toxoid. They attempted to redesign PLGA microspheres by co-encapsulating together with tetanus toxoid in the dry solid state together with potential stabilizers such as the haloes, bovine serum albumin, alginate, heparin, dextran or poloxamer 188 by employing an appropriate technique. The PLGA microspheres were able to release in vitro antigenically active tt for at least 5 weeks. The efficacy of the strategy was demonstrated by high, long lasting, titers of neutralizing antibodies achieved after in vivo administration of dextran containing microspheres with a small amount of alum adsorbed tetanus toxoid as compare to the commercial absorbable tetanus toxoid vaccine. The findings suggested that future developments in the area of vaccinology depended on the ability to combine a detailed knowledge if the microencapsulation technology with rational choice of stabilizing excipient or combination of excipients. Phillippe Bouillot et al, (1999) prepared MPOE – PLA microspheres containing bovine serum albumin (BSA) by double emulsion method. They observed high encapsulation efficiency with double emulsion method. The atomic force microscopic analysis showed the presence of MPOE chains, which led to rough particle surfaces. The diffusion of 1% rhodamine
aqueous solution into the microspheres by means of conofocal microscopy showed a fast diffusion of water through the matrices containing high molecular weight MPOE chains and explained the fast release of BSA from the microspheres. Stenekes and Hennink (1999) demonstrated the equilibrium water content of microspheres with a hydrogel character based on cross-linked dextran. The water content was established by determination of the increase in blue dextran concentration after incubation of this solution with dried microspheres. An excellent correlation between the actual and predicted water contents was observed for microspheres with a moderate to high cross-link density. On the other hand, for particles with low cross-link density, the equilibrium water content was higher than predicted. Smooth, highly spherical, cross linked chitosan microspheres in the size range of 45–300 mm loaded with progesterone were prepared by glutaraldehyde crosslinking of an aqueous acetic acid dispersion of chitosan containing progesterone in a non-aqueous dispersion medium consisting of liquid paraffin and petroleum ether stabilized using sorbitan sesquioleate (Jameel et al, 1998). Data obtained suggested that the crosslinked chitosan microspheres would be an interesting system for long term delivery of steroids.

The modified chitosan sponges were found to be effective as sustained release drug carrier (Muller et al, 1997). Micronized triamcinolone acetonide was used as a model drug. The drug releasing from the N-acetyl chitosan and the cross linking sponges was pH dependent. The drug release was greatly influenced by pH, the drug release at pH 1.2 was faster than at pH 7.4. The water uptake of chitosan sponges was more than 20 times of their weight. The delayed drug release depends on the density of cross linking agent and microparticle size. The possibility of inducing antigen – cytotoxic T lymphocytes (CTL) responses in vivo with a short synthetic peptide from the circum sporezotic protein of Plasmodium berghei 252 – 260 by using different
microspheres formulations was demonstrated by Ying men et al, 1997. They concluded that microspheres, the potent antigen delivery system could stimulate CTL response. James Anderson and Mathew Shive (1997) reviewed that a fundamental understanding of the in vivo biodegradation phenomenon as well as an appreciation of cellular and tissue responses which determine the biocompatibility of biodegradable PLA and PLGA microspheres are important components in the design and development of biodegradable microspheres containing bioactive agents for therapeutic application. Justin Hanes et al (1997) reviewed that polymer microspheres have shown great potential as a next generation adjuvant to replace or complement existing aluminum salts for vaccine potentiation. Microsphere-based systems could be made to deliver subunit protein and peptide antigens in their native form in a continuous or pulsatile fashion for periods of weeks to months with reliable and reproducible kinetics, often obviating the need for booster immunizations in animal models.

Changhong et al (1995) made biodegradable micropraticles of poly (lactide-co-glycolide) (PLG). These were used for protracted and pulsed release of incorporated ricin toxoid (RT) vaccine to reduce the multiple immunization doses and the time required to induce complete protection against lethal aerosol-borne rich challenge. An early (3 weeks) and long lasting (1year or longer) antigen - antibody response was evoked by a single administration of encapsulated RT vaccine. In contrast three administrations of the aqueous RT were required to stimulate similar antibody response. These results demonstrated the usefulness of biodegradable microparticles to improve the efficacy of the immunization with RT vaccine and probably many other vaccines as well. Akbuga et al (1994) prepared microspheres containing furosemide from W / O emulsion system using liquid paraffin as an
external phase and a solution of chitosan in acetic acid as a disperse phase. The microspheres having 360-690μm in diameter were obtained by them. The microsphere properties were affected by the type and concentration of chitosan, drug, concentration, cross linking process, and the viscosity of oil and stirring rate during the preparation. Dissolution data indicated that the release followed the Higuchi matrix model.

Jameela et al (1994) developed a new technique whereby bovine serum albumin and diptheria toxoid were loaded by passive absorption from aqueous solutions into preformed glutaraldehyde cross linked chitosan microspheres in vitro release under skin conditions showed that even though there was a large burst effect, there was more or less steady increase with time after several days. Biodegradation was not complete in 6 months demonstrating the potential of cross linked chitosan microspheres as a long-acting drug delivery vehicle. Polk et al (1994) prepared microcapsules containing the polysaccharide chitosan reacted with sodium alginate in the presence of calcium chloride and reported that the pH of extra capsular environment affected the release of albumin ova 24 hrs at pH 3.0 and 73% release was obtained at pH 8. The albumin release was increased by decreasing molecular weight. So the capsule produced with the lower molecular weight gave better results. The development of single-dose vaccines, mainly those administered during childhood, which would effectively protect against certain diseases, would be a very important advance towards better immunization coverage and protection against the respective pathogens. Biodegradable polymeric microspheres, which are 'programmed' to deliver the antigen when a boost of the immune response is required (Aguado, 1993). William et al (1994) reported that the biodegradable polymeric microspheres were suited for preprogrammed release of contraceptive steroids and had significant
potential for adaptation to antigen release for immunization, with the size of the polymer particles ranging from 1 to 300 μm. The most studied polymer for the controlled release of pharmacological agents is made from lactic acid and glycolic acids. These polymers are used as absorbable structure materials. The lack of toxicity of this poly (lactide-co-glycolide) polymer has been established by FDA licensure. Jeffery et al (1993) used solvent evaporated technique to prepare poly (lactide-co-glycolide) (PLGA) microparticles and investigated the effect of various process parameters on particles size. Particles of below 3μm of mean particle size were prepared by using a relatively small amount of polymer, at high stirring rate and low volume of aqueous phase containing high concentration of surfactant.

Miscellaneous

Adjuvants and antigen delivery systems are essential in inducing and modifying immune responses (Tazio Stormi et al, 2005). They reviewed the cellular and molecular factors involved in the induction of immunity and how the factors might influence the potency of an adjuvant or a vaccine. Despite two centuries of vaccine use, only few adjuvants and delivery systems are licensed for human use. This is partly because traditional vaccines based on attenuated live organisms and their invasiveness provides efficient delivery to antigen – presenting cells and various natural occurring components of the pathogens stimulate the immune system (Achal Pashine et al, 2005).

Susan Robertson et al, (2002) reviewed that the WHO vaccine trial registry prospectively registered clinical vaccine studies supported by World Health Organization. During December 1999, 103 studies from 43 countries with nearly 80% in developing countries were included in the WHO trial registry. The registry documented an expanding research capacity with an average of 3.9 new studies per
year during 1987 – 1993, raise to 10.7 per year during 1994 – 2000. The studies were focused on broad spectrum of infectious organisms, which included clostridium tetani, dengue virus, enterotoxigenic Escherichia coli, Haemophilus influenzae type B, hepatitis B virus, Measles virus, Mycobacterium tuberculosis, Nisseria meningitidis, polio virus, respiratory syncitial virus, Rota virus, Salmonella typhi, Shigella, Streptococcus pneumoniae and Vibrio cholerae. John Cox and Alan Coulter (1997) revived the classification of adjuvants and there mode of action. They deeply discussed a range of both substances and processes which when added to performed upon a vaccine would increase its immunogenicity. They also stated that many new vaccines are under developments and to simplify, vaccination schedules both by increasing the number of components per vaccine and decrease in the no of doses required for vaccine course. Rajesh Gupta and George Siber (1995) reviewed that in recent years, adjuvants received much attention because of the development of purified, subunit and synthetic vaccines, which are poor immunogens and require adjuvants to evoke the immune response. The adjuvants can modulate the immune response by stimulating major histocompatibility complex (MHC) class I or MHC class II and Th₁ or Th₂ type, which is very important for protection against various pathogens.