CHAPTER I
INTRODUCTION

Rapid and exciting research breakthroughs in the fields of immunology and molecular biology in recent years have greatly enhanced the potential for developing new vaccines or improving existing ones. The resulting rising number of diseases that can be prevented by vaccination, coupled with the growing trend of preferring cost-effective preventive medical interventions over expensive therapeutic modalities, has increased the complexity of administering to all those who need them, the many different vaccines that will soon be available (André, 1994). The continuing increase in the number of effective vaccines suitable for use in infancy and early childhood has posed substantial economic and logistic difficulties. Providing these vaccines as separate injections not only is expensive but also requires multiple needle sticks, distressing parents, providers, and patients alike. Scheduling additional vaccination visits to reduce the number of injections per visit increases costs, burdens staff, and jeopardizes the entire immunization program by increasing the likelihood of missed vaccinations. The shipping, handling, and storage of a plethora of vaccines are burdensome and expensive and increase the possibility of error (Decker, Edwards and Bogaerts, 2004). Hence attention in the field of vaccinology is now focusing on the development of combined vaccines.

The availability of combined vaccines containing protective antigens against all diseases for which universal immunization is recommended would simplify the implementation, increase the acceptance, and lower the cost of global immunization programs.

The use of combined vaccines will increase convenience of vaccine delivery and thus improve compliance in a population. It will also reduce the cost of vaccine administration. Fewer inoculations will be needed to protect against more diseases, thus enhancing the acceptance of immunization programs by both the general public and medical profession. These cumulative favorable factors will boost the effectiveness and success of immunization programs by increasing vaccine coverage, while at the same time creating cost savings in healthcare budgets. It must not be forgotten that the logistical costs of vaccine delivery are usually much greater than the

price of the vaccines used. Thus the availability of more polyvalent combined vaccines will reduce the overall financial expenditure of immunization programs even if combined vaccines are more expensive than the sum of the prices of their separate components (André, 1994).

The combining of multiple related or unrelated antigens into a single vaccine is not a new concept; combination vaccines have long been a bedrock of our pediatric and adult immunization programs. Those combination vaccines in common use include diphtheria and tetanus toxoids, available alone (DT or Td) or with whole-cell (DTwP) or acellular (DTaP) pertussis vaccine; inactivated (IPV) or live oral (OPV) trivalent poliovirus vaccine; and measles and rubella vaccine, available alone (MR) or with mumps vaccine (MMR) (Decker, Edwards and Bogaerts, 2004). Over the last ten years, SmithKline Beecham Biologicals (SB BIO), the vaccine manufacturer that employs the author, has been engaged in developing new pediatric vaccines using DTP as the cornerstone on which to build more polyvalent-vaccines. The difficulties encountered, progress made, results obtained and lessons learned will be surveyed, in chronological fashion (André, 1999).

Possible approaches towards combined vaccines. In the near term, conventional methods of mixing existing live vaccines or killed antigens will be favoured. There are already combined live vaccines that exist and have been used for some time, such as trivalent oral polio and measles, mumps, rubella (MMR) vaccines. Combined killed vaccines based on mixtures of killed antigens are conceptually more promising. Substantial attention is being given to the killed combined diphtheria, tetanus and pertussis (DTP) vaccine which has been administered to infants for over five decades as a building block for many future combined vaccines. Either the classical DTP with a whole-cell pertussis component (DTPw), or a new less reactogenic and more immunogenic DTP with an acellular pertussis component (DTPa), could be used as the foundation for new combined vaccines. Antigens that have been added to this DTP core include those for hepatitis B (DTPw-HBV), inactivated polio vaccine (DTPw-IPV, already used for some time in some countries), Haemophilus influenzae type b (HIB), now recommended for universal vaccination of babies (DTPw-HIB), or eventually a combination of all of these (DTP-HBV-IPV-HIB). These combined vaccines will become even more polyvalent as and when new

vaccines are developed in the future, possibly against diseases such as hepatitis C, respiratory syncytial virus (RSV), cytomegalovirus, Lyme, herpes, rotaviruses, arboviruses or Japanese encephalitis virus (JE).

The number of different vaccine combinations that can be created with just a few additional antigens is considerable. By adding 1 to 4 other antigen components (e.g. HIB (freeze-dried or liquid), HBV, IPV, and HAV) to either DTPw or DTPa, there are 44 possible different vaccine combinations that can be generated. This number would increase to thousands if individual components from different manufacturers were considered. As every individual new combined vaccine (taking into account differences in components according to source) must be developed separately to demonstrate safety, stability, compatibility and efficacy, the development of all these vaccines becomes prohibitive in terms of cost (André, 1994). No information was found in the literature of combined DTPw-JE vaccine which JE vaccine is widely used in Asia for childhood immunization and also used for travelers to Asia from other parts of the world and because of DTP vaccine and JE vaccine were produced in country. In this study, the processing variables were investigated for DTP-JE preparation.

Objectives of the study

The aims of this study were as the following:

1. To conceptually develop combined DTP-JE vaccine.
2. To study the adsorption of diphtheria toxoid, tetanus toxoid and JE antigen on aluminium hydroxide adjuvant by consider the adsorptive capacity value of each antigen.
3. To determine the adsorption of diphtheria toxoid, tetanus toxoid and JE antigen on aluminium hydroxide adjuvant by investigate the effect of mixing speed mixing time and temperature of these antigens.
4. To compare the antigens content from different formulation processes of combined preparations and observe for the antigens content, characterization and morphology after formulate.
5. To evaluate the physical stability of combined DTP-JE preparations.