Formulation of Inactivated Polio Vaccine for Thermal Stability

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ABSTRACT SUMMARY
Polio eradication and post-eradication programs require cost-effective methods of mass vaccination. We are developing microneedle patches to simplify vaccination and reduce costs. Here, we studied formulations that stabilize inactivated polio vaccine during drying and storage, and found that formulation with maltodextrin and ovalbumin retained full stability after 4 weeks storage at 22°C and maintained 60% stability after 4 weeks storage at 40°C. On-going research seeks to provide still greater stability for longer times.

INTRODUCTION
Eradication of wild-type poliovirus is being pursued with oral polio vaccine (OPV), which is facilitated by simple mass vaccination by minimally trained personnel, often door-to-door [1]. However, OPV vaccination carries the risk of virus mutation into a virulent form. Thus, post-eradication efforts to control vaccine-derived polio require the use of inactivated polio vaccine (IPV), which does not carry this risk. However, IPV administration is costly, because it requires expert personnel to give the vaccine at central locations, thereby increasing cost and complexity of vaccination campaigns.

We are developing a microneedle patch that enables simple IPV mass vaccination by minimally trained personnel. To further simplify vaccination campaigns and reduced costs, we seek to formulate the patch to stabilize IPV for storage without refrigeration. This is a significant challenge given that commercial IPV is formulated as a liquid that is stored under refrigeration, because it is not generally stable upon drying or storage at elevated temperature. Because microneedle patches are solid-state devices, this project seeks to stabilize IPV during drying and storage at elevated temperature.

EXPERIMENTAL METHODS
To identify suitable formulations to stabilize IPV during drying and storage, we screened 60 different GRAS excipients, including biocompatible natural and synthetic polymers; oligomers; mono-, di- and polysaccharides; sugar alcohols; amino acids; vitamins; and salts, as listed in Table 1.

Each individual excipient was formulated with IPV (IPOL, Sanofi Pasteur) in liquid solution, placed in 96-well plates and air-dried at room temperature overnight until the water content was less than 8 wt% of the total mass of the formulation on a dry basis. For mixed formulations, we selected excipients that maintained stability greater than 40% after 1 week storage at 40°C, and mixed them at a 1:1 mass ratio.

RESULTS AND DISCUSSION
To study stability during storage, the formulations dried as a thin film inside the wells were packaged with nitrogen and desiccant, stored at 40°C for up to 4 weeks, and then reconstituted at different times for ELISA assay (using antibody for type 2 IPV). The percentage stability of IPV in the formulation was calculated in comparison with non-processed liquid IPV.

Table 1. List of excipients

<table>
<thead>
<tr>
<th>Type</th>
<th>Excipient</th>
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<tbody>
<tr>
<td>Polymer</td>
<td>Amylopectin, Bovine serum albumin, Carboxymethylcellulose, Chondroitin Sulfate, Dextran, Dextran Sulfate, Dextrin, Inulin, Ovalbumin, Polyethylene glycol, Polyvinyl alcohol, Polyvinylpyrrolidone, Soy Protein</td>
</tr>
<tr>
<td>Oligomer</td>
<td>Cyclodextrin, Maltodextrin</td>
</tr>
<tr>
<td>Sugar</td>
<td>Fructose, Galactose, Glucose, Trehalose, Sucrose, Maltose, Lactose, Raffinose</td>
</tr>
<tr>
<td>Sugar</td>
<td>Erythritol, Threitol, Xylitol, Arabitol, Ribitol, Mannitol, Sorbitol, Dulcitol, Inositol, Maltitol</td>
</tr>
<tr>
<td>Amino Acid</td>
<td>Alanine, Glycine, Proline, Cysteine, Serine, Threonine, Arginine, Lysine</td>
</tr>
<tr>
<td>Vitamin</td>
<td>Thiamin, Riboflavin, Nicotinamide, Pantothenic acid, Biotin, Folic acid, Ascorbic acid</td>
</tr>
<tr>
<td>Salt</td>
<td>Al(OH)3, MgCl2</td>
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Traditional excipients used as stabilizers in many other kinds of formulations, like sugars and sugar alcohols, showed good ability to maintain the integrity of IPV upon drying, but most of them showed significant loss in IPV stability after the formulation was stored at 40°C (data not shown). In contrast, polymer excipients generally showed substantial loss upon drying, but less degradation rate than sugar and sugar alcohol molecules during storage at 40°C (data not shown). Some excipients used to stabilize IPV in liquid formulation such as MgCl₂, deuterium oxide, sucrose were not able to effectively maintain the integrity of IPV during drying and storage period (data not shown).

Regarding maltodextrin (DE 13), it showed better capability than high molecular weight molecules such as maltodextrin (DE 4) and dextrin, as shown in Fig 1c and 1d, but smaller maltodextrin (DE 17) was not as good as maltodextrin (DE 13; data not shown), probably suggesting that maltodextrin may provide the optimal size for interaction to stabilize IPV.

Given its very different structure, ovalbumin may provide a different mechanism of maintaining the integrity of IPV compared to maltodextrin or other polysaccharides, although this mechanism is not currently clear. However, co-formulation of ovalbumin with maltodextrin showed significantly better stabilization than each single formulation, presumably indicating that second excipient may enhance the function of first one and/or they have their own mechanisms of action that act in combination.

CONCLUSION

IPV formulated with maltodextrin (DE 4 and 13), dextrin, and ovalbumin maintained IPV stability of approximately 50% of the positive control after 1 week at 40°C. The two-excipient formulation of maltodextrin DE 13 and ovalbumin maintained 100% stability after 4 weeks storage at room temperature and maintained 60% stability after 4 weeks storage at 40°C. On-going studies seek to optimize the formulation further in order to enable long-term storage of IPV without refrigeration.

REFERENCES

ACKNOWLEDGMENTS
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