

OptiPrep™ Mini-Review MV06

Purification and analysis of hepatitis C virus and other Group IV viruses

- ◆ This Mini-Review principally provides in **Section 2** a bibliography of all those papers reporting the use of OptiPrep™ in the purification and analysis of Group IV viruses. A short **Section 1** briefly summarizes the gradient strategies that have been used and the advantages of using OptiPrep™.
- ◆ **Section 1** concludes with a list of all the relevant OptiPrep™ Application Sheets that are currently available for research on hepatitis C virus and other Group IV viruses, and how this information is accessed.
- ◆ The format for **Section 2** is described in the introduction to the section.

1. Introduction

1-1. Technical background to the use of OptiPrep™

In all comparative studies between CsCl and iodixanol, the recovery of virus infectivity is much higher and the particle:infectivity ratio much lower when viruses are purified in iodixanol. Although sucrose is generally less deleterious to viral infectivity than CsCl, it can nevertheless also have serious effects on certain important aspects of viral function; in particular the loss of surface glycoproteins from retroviruses has been noted [1]. This may be related to its viscosity, which, in solutions of the same density, is much higher than that of iodixanol. Most iodixanol gradients can also be made isoosmotic over the entire density range.

Like CsCl, sucrose must be dialyzed before infectivity can be measured. In contrast both infectivity measurements using cultured cells and many add-on techniques can be performed without dialysis of iodixanol. Combined with the availability of OptiPrep™ as a sterile solution, this makes the use of OptiPrep™ for virus purification and assembly analysis much more convenient than the use of either CsCl or sucrose. The only analytical technique for which removal of the iodixanol is essential is electron microscopy. Consequently iodixanol is being increasingly used for the purification of hepatitis C virus particles from lysed cultured cells, from conditioned culture medium or from plasma samples from infected patients.

1-2. Solution preparation

Isoosmotic solutions for making gradients may be prepared simply by diluting OptiPrep™ with either Tris- or HEPES-buffered sucrose [2] or NaCl [3] solutions. Sometimes bovine serum albumin is included [3].

1-3. Gradient strategy

A wide range of density gradient strategies is available; most of the separations are based on buoyant density and both sedimentation and flotation formats have been reported. Continuous 10-40% (w/v) iodixanol gradients, with the crude virus-containing sample top-loaded [3] or discontinuous gradients of 10, 20, 30 and 40% (w/v) iodixanol, with the crude virus in the densest layer [4] have been run in routine swinging-bucket rotors. Centrifugation is normally carried out for at least 6 h at 150-200,000 *g* but lower *g*-forces for longer times are not uncommon. The flotation mode offers the advantage of easy handling of virus that has been concentrated on to a cushion of a dense iodixanol solution [5]. Virus particle size has also been estimated by sedimentation through 4-24% (w/v) iodixanol gradients [6].

Hepatitis C virus particles have also been analyzed in self-generated gradients of iodixanol [7]. This very simple technique, which has been used for a number of other viruses, requires only adjustment of the crude virus suspension to 25% (w/v) iodixanol. The formation of a self-generated gradient is most efficiently carried out in a vertical or near-vertical rotor at approx 350,000 *g* for 2-3 h but a fixed-angle rotor (approx. 10 ml tube size) may be substituted for longer times. The low virus concentration at the start of the centrifugation and the lack of any liquid/liquid interfaces may optimize resolution of virus particles from contaminants.

- ◆ Large-scale production of virus has been addressed in ref 8

1-4. References

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2. **Nielsen, S.U.**, Bassendine, M.F., Burt, A.D., Martin, C., Pumeechockchai, W. and Toms, G.L. (2006) *Association between hepatitis C virus and very-low-density lipoprotein (VLDL)/LDL analyzed in iodixanol density gradients* J. Virol., **80**, 2418-2428
3. **Lindenbach, B.D.**, Evans, M.J., Syder, A.J., Wolk, B., Tellinghuisen, T.L., Liu, C.C., Maruyama, T., Hynes, R.O., Burton, D.R., McKeating, J.A. and Rice, C.M. (2005) *Complete replication of hepatitis C virus in cell culture* Science, **309**, 623-626
4. **Steinmann, E.**, Brohm, C., Kallis, S., Bartenschlager, R. and Pietschmann, T. (2008) *Efficient trans-encapsidation of hepatitis C virus RNAs into infectious virus-like particles* J. Virol., **82**, 7034-7046
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7. **Nielsen, S.U.**, Bassendine, M.F., Martin, C., Lowther, D., Purcell, P.J., King, B.J., Neely, D., Toms, G.L. (2008) *Characterization of hepatitis C RNA-containing particles from human liver by density and size* J. Gen. Virol., **89**, 2507-2517
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1-5. OptiPrep™ Application Sheets

Detailed protocols for the isolation of the hepatitis C virus (*Flaviviridae*) may be accessed from the OptiPrep™ Applications flash-drive or from the following website: www.axis-shield-density-gradient-media.com, click on “Methodology” then “Viruses” to open up the Virus Index. Other relevant OptiPrep™ Application Sheets may also be accessed from the top of the Index.

◆ <i>Flaviviridae</i> - pre-formed gradient	OptiPrep™ Application Sheet V19
◆ <i>Flaviviridae</i> - self-generated gradient	OptiPrep™ Application Sheet V20
◆ Other Group IV viruses	OptiPrep™ Application Sheets V21 & V22
◆ Preparation of density gradient solutions	OptiPrep™ Application Sheet V01
◆ Preparation of continuous and discontinuous gradients	OptiPrep™ Application Sheet V02
◆ Preparation of self-generated gradients	OptiPrep™ Application Sheet V03
◆ Harvesting gradients	OptiPrep™ Application Sheet V04
◆ Analysis of gradients	OptiPrep™ Application Sheet V05
◆ Concentration of virus samples	OptiPrep™ Application Sheet V06

2. Bibliography

- ◆ This bibliography provides a comprehensive reference list of all the papers reporting the use of OptiPrep™ for purification of Group IV viruses, published before the end of November 2017.
- ◆ Viruses are listed alphabetically according to **family and virus type**
- ◆ References are also divided alphabetically into **“Research topic” sections and subsections**.
- ◆ All references are listed alphabetically according to **First Author**
- ◆ To aid selection, key words in the titles are highlighted in light blue.

2-1. Arteriviridae

Porcine reproductive and respiratory syndrome virus

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2-2. Caliciviridae

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2-3. Coronaviridae

2-3-1. Middle East respiratory syndrome virus

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2-3-2. SARS-Coronavirus

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2-4. Flaviviridae

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2-4-2 Dengue virus

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2-4-3. Hepatitis C

2-4-3-1. Antimicrobial peptides

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2-4-3-2. Anti-scavenger receptor (B type)

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2-4-3-3. Assembly and cellular release of virus particles

2-4-3-3a. Apolipoprotein/lipoprotein, influence of

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2-4-3-3b. Lipid droplets

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2-4-3-3c. Lipids, influence of

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2-4-3-3d. Intracellular membrane compartments

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2-4-3-3e. Protein/glycoprotein interactions

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2-4-3-3f. Proton channel

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2-4-3-3g. Release inhibition

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2-4-3-3h. RNA-related effects

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2-4-3-4. Cell entry/virus fusion/virus transmission

2-4-3-4a. Inhibitors/markers

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