

Cascadeflo™ EC

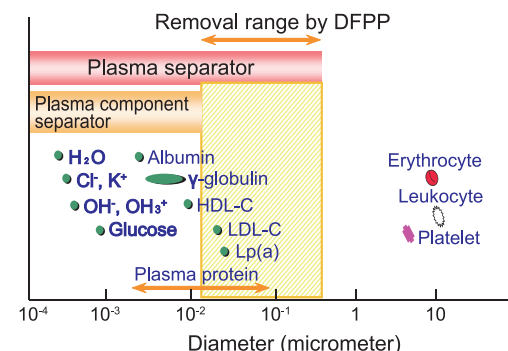
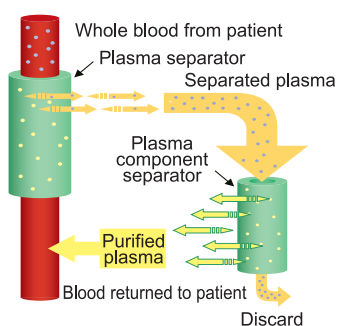
Asahi Plasma Component Separator
for Double Filtration Plasmapheresis (DFPP)

Minimal albumin loss & effective removal of target substances by selection of appropriate filter among the four different pore size models

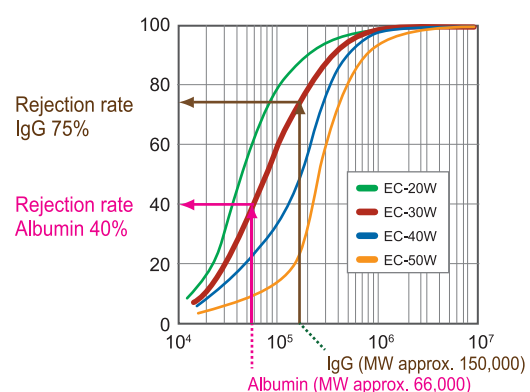


Separation Mechanism

Plasma, obtained by Plasmaflo OP is then fractionated into large and small molecular weight components by Cascadeflo EC. Large molecular weight components including pathogenic substances such as IgG and LDL-C are discarded. Small molecular weight components including valuable substances such as albumin are returned to the patient.



Selection of Models



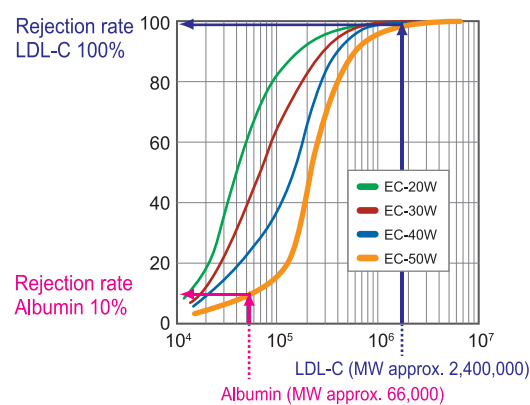
Use of EC-30W

EC-30W is used mainly for IgG removal. 75% of IgG can be removed using EC-30W based on the rejection rate of IgG (molecular weight (MW) approx. 150,000).

Since 40% of albumin (MW approx. 66,000) is removed, replacement fluid such as albumin solution is necessary to compensate for the removed albumin.

Note: EC-20W has a higher removal performance than EC-30W, and a higher possibility of filter clogging. Albumin removal is higher, and a larger amount of replacement fluid is necessary.

In vitro data
Plasma flow rate: 30mL/min
Discard flow rate: 6mL/min



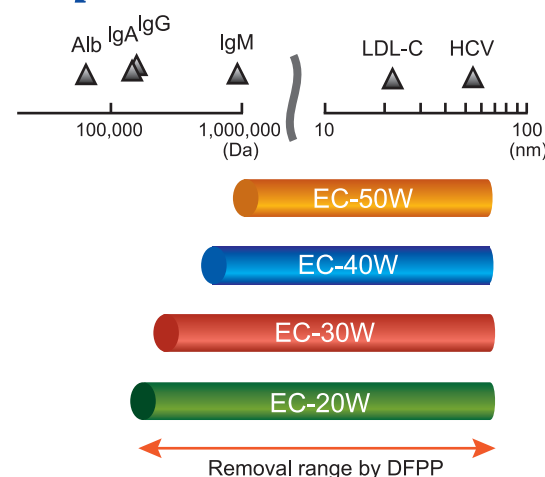
Use of EC-50W

EC-50W is mainly used for LDL-C removal.

Approx. 100% of LDL-C can be removed using EC-50W based on the rejection rate of LDL-C (MW approx. 2,400,000). Albumin removal is only 10%, and albumin replacement is NOT necessary.

In vitro data
Plasma flow rate: 30mL/min
Discard flow rate: 6mL/min

Replacement Fluid



Model	Practical example of replacement fluid condition
EC-50W	Not necessary
EC-40W	Discard 0 - 10% of processed plasma, replace with equivalent volume of saline solution. Take care of albumin level when treatments are performed every day or every other day.
EC-30W	Discard 10% of processed plasma, replace with equivalent volume of 5% albumin solution.
EC-20W	Discard 20% of processed plasma, replace with equivalent volume of 12% albumin solution.

Specifications

	EC-20W	EC-30W	EC-40W	EC-50W
▲ Hollow fiber Material	Ethylene vinyl alcohol copolymer			
Inside diameter	175µm			
Wall thickness	40µm			
Surface area	2.0m ²			
priming volume	150mL			
▲ Container Material	Polycarbonate			
Dimensions	280mm[L] x 57mm[D]			
▲ Sterilization	Gamma-Ray			

EC-20W is the smallest pore size model, and EC-50W is the largest pore size model

References

- Julius et al. The Dresden Apheresis Center - experience with LDL apheresis and immunoabsorption. *Atheroscler Suppl.* 10:12-6,2009.
- Hovland et al. Patient tolerance regarding different low-density lipoprotein apheresis columns: frequent minor side effects and high patient satisfaction. *J Clin Lipidol.* 5:45-9,2011.
- Kamstrup et al. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. *Circulation.* 117:176-84,2008.
- Jaeger et al. Longitudinal cohort study on the effectiveness of lipid apheresis treatment to reduce high lipoprotein(a) levels and prevent major adverse coronary events. *Nat Clin Pract Cardiovasc Med.* 6:229-39,2009.
- Leebmann et al. Lipoprotein apheresis in patients with maximally tolerated lipid-lowering therapy, lipoprotein(a)- hyper lipoproteinemia, and progressive cardiovascular disease: prospective observational multicenter study. *Circulation.* 128: 2567-76,2013.
- Hirai et al. Significance of low-level DSA detected by solid-phase assay in association with acute and chronic antibody-mediated rejection. *Transpl Int.* 25:925-34,2012.
- Yamaji et al. Long-term clinical outcomes of synchronized therapy with plasmapheresis and intravenous cyclophosphamide pulse therapy in the treatment of steroid-resistant lupus nephritis. *Ther Apher Dial.* 12:298-305,2008.
- Liu et al. Successful treatment of patients with systemic lupus erythematosus complicated with autoimmune thyroid disease using double-filtration plasmapheresis: a retrospective study. *J Clin Apher.* 26:174-80,2011.
- Kasuya et al. Clearance efficacy of autoantibodies in double filtration plasmapheresis for pemphigus foliaceus. *Acta Derm Venereol.* 93:181-2,2013.
- Kitabata et al. Double filtration plasmapheresis for the treatment of bullous pemphigoid: a three case report. *Ther Apher.* 5:484-90,2001.
- Weiss. A critical review on the use of lipid apheresis and rheopheresis for treatment of peripheral arterial disease and the diabetic foot syndrome. *Semin Dial.* 25:220-7,2012.
- Ferrannini et al. Rheopheresis in vascular diseases. *Int J Artif Organs.* 30:923-9,2007.
- Klingel et al. Rheopheresis in patients with ischemic diabetic foot syndrome: results of an open label prospective pilot trial. *Ther Apher Dial.* 7:444-55,2003.
- Kim et al. Double-filtration plasmapheresis for the treatment of patients with recalcitrant atopic dermatitis. *Ther Apher Dial.* 17:631-7,2013.
- Isoda et al. Microscopic polyangiitis complicated with cerebral infarction and hemorrhage: a case report and review of literature. *Nihon Rinsho Meneki Gakkai Kaishi.* 33:111-5,2010. JAPANESE
- Zhang et al. Comparison of double filtration plasmapheresis with immunoabsorption therapy in patients with anti-glomerular basement membrane nephritis. *BMC Nephrol.* 15:128,2014.
- Koss et al. Prospective, randomized, controlled clinical study evaluating the efficacy of Rheopheresis for dry age-related macular degeneration. *Dry AMD treatment with Rheopheresis Trial-ART. Graefes Arch Clin Exp Ophthalmol.* 247:1297-306, 2009.

Indication

This device is applicable to diseases which have the causative factors or etiology in high molecular weight substances of plasma, such as

- metabolic diseases with EC-50W or EC-40W
- autoimmune diseases with EC-30W or EC-20W

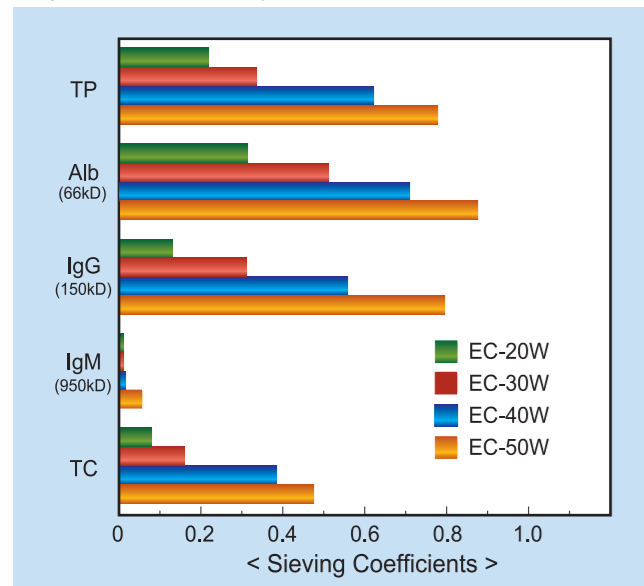
Features of Cascadeflo EC

- Wide applications by selection of optimal model
- Minimal loss of patient's own desirable non-pathogenic substances, e.g., albumin
- No or minimal risk of infection from replacement fluid
- Reduces possible protein allergy to replacement fluid

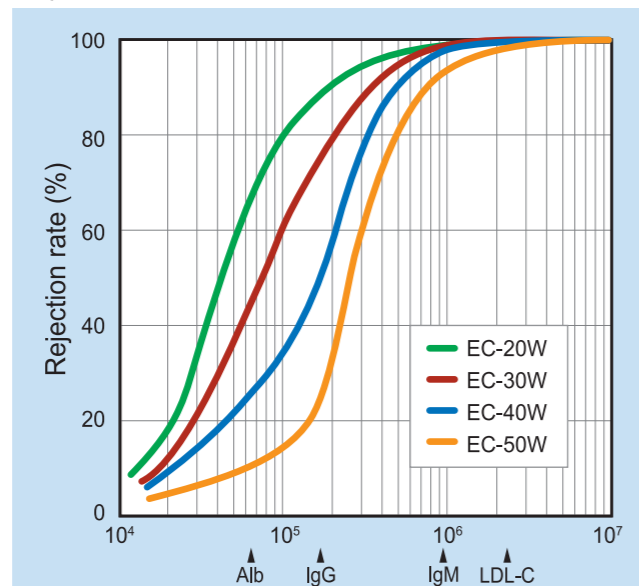
Sharp Cut-off Curve

Homogeneous distribution of pore size provides sharp cut-off feature

a) Permeability



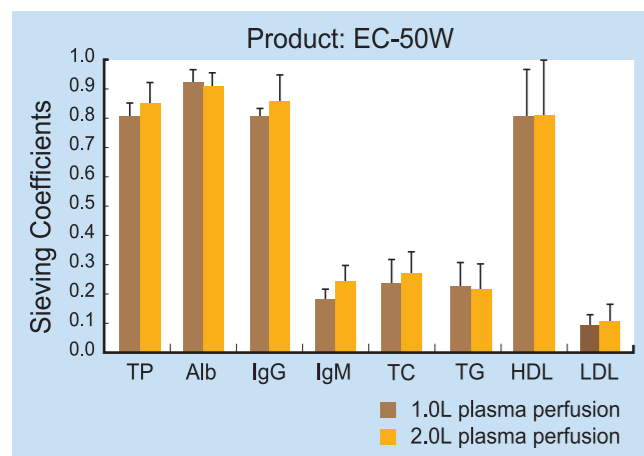
b) Cut-off Curve



in vitro data
Plasma flow rate : 30mL/min
Dicard flow rate : 6mL/min

Stable Sieving Coefficient

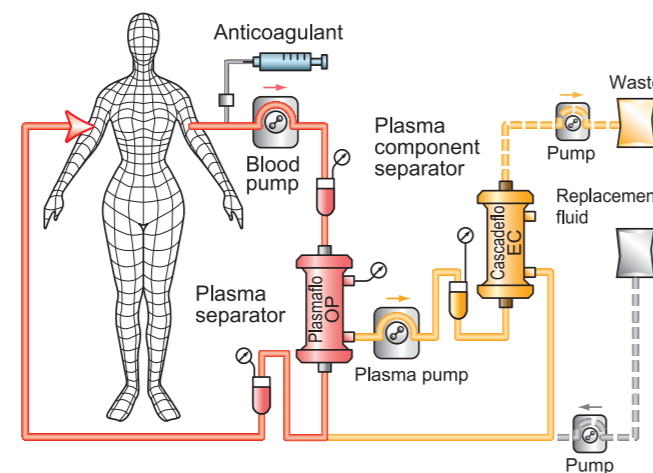
Unique microstructure of hollow fiber avoids clogging, and enables stable performance



in vivo data
Blood flow rate : 100mL/min, Plasma flow rate : 25mL/min
Dicard flow rate : 2.5mL/min

(Data from Shinseikai Daiichi Hospital, Japan)

Circuit Diagram



Clinical Experiences of DFPP

<Metabolic Disorders>

Familial hypercholesterolemia (FH)

LDL apheresis is applied for FH patients who have either ineffective or ill tolerated maximum medication therapy and ineffective dietary control. LDL cholesterol (LDL-C) can be removed from plasma by adsorption, precipitation, or filtration devices or from whole blood. All LDL apheresis methods are effective in reducing LDL-C levels [1]. A study compared three different LDL apheresis columns (DL-75, LA-15, EC-50W) with respect to side effects (SE) in three cases with FH who went through six treatments with each of the aforementioned methods, finding a significant fewer SE with Cascadeflo EC-50W after apheresis [2].

Lp(a) hyperlipoproteinemia

Lp(a) is a circulating lipoprotein that resembles LDL-C. Increasing levels of Lp(a) increase in risk of myocardial infarction [3]. Beneficial effect of LDL apheresis in the incidence of major adverse coronary events (MACE) was observed in the retrospective study [4]. Incidence of MACE in patients who have elevated Lp(a) level was evaluated for two years before and after commencement of LDL apheresis in the prospective observational multicenter study. 101 cases with DFPP were enrolled. Incidence of MACE was significantly decreased from 0.52 in the last year before commencement of DFPP to 0.12 in the first year of DFPP ($p < 0.0001$) [5].

<Organ Transplant>

HLA-/ABO-incompatible kidney transplant

DFPP is an established modality of anti-HLA antibody and anti-blood group removal in HLA-incompatible and ABO-incompatible kidney transplant. Antibody mediated rejection (AMR) is an important cause of acute and chronic allograft dysfunction and graft loss. Desensitization protocol including DFPP and rituximab before transplant was performed in 52 cases with HLA-incompatible living donor kidney transplant. The incidence of acute and chronic AMR was significantly reduced ($p = 0.005$ and $p = 0.004$, respectively) compared to 24 cases who did not receive desensitization. The graft survival rate was improved to comparable to HLA-compatible cases [6].

<Rheumatologic Disorders>

Systemic lupus erythematosus (SLE)

DFPP is effective for eliminating pathogenic molecules such as anti-DNA antibody and immune complexes in SLE patients. Clinical benefit of apheresis (DFPP or immunoadsorption) was evaluated in lupus nephritis (LN) patients in three groups, i.e., apheresis group (9 cases), intravenous cyclophosphamide pulse therapy (IVCY) group (16 cases), and combination of apheresis and IVCY group (13 cases). Complete remission rate was comparable in apheresis and IVCY groups, while combination group had higher complete remission rate. Combination therapy may be superior in achieving the complete remission of LN, and in minimizing the risk of adverse effects of IVCY [7]. 11 patients with lupus complicated with autoimmune thyroid disease underwent a cycle of DFPP, showing an evident improvement of antithyroid antibodies and lupus activity [8].

<Dermatologic Disorders>

Pemphigus, Pemphigoid

Pemphigus is an autoimmune skin blistering disease in which desmoglein, an epidermal cell adhesion molecule is targeted by autoantibodies. Pemphigoid is an autoimmune skin blistering disease caused by antidermal basal lamina antibody. Medication in Pemphigus and Pemphigoid includes the administration of corticosteroids, immunosuppressants and IVIg. DFPP is applied for patients who is resistant to medication or patients suffering from complications of medication. 2 cases in pemphigus [9] and 3 cases in pemphigoid [10] received series of DFPP, resulted in an improvement in clinical symptoms and remission.

<Microcirculatory Disorders>

Peripheral arterial disease (PAD)

By eliminating LDL-C particles and high molecular weight proteins, DFPP decreases plasma viscosity and thereby improves hemorheology in microcirculation [11]. In 5 cases suffering from PAD and uremia, three cases experienced a complete remission of ulcers and the other two cases had a partial remission of ulcers after a cycle of 10 DFPP sessions, without manifesting any adverse effects [12]. 8 cases with non-healing foot ulcers caused by severe ischemic diabetic foot syndrome underwent 7 DFPP sessions. Wound healing was accelerated in 4 cases and was unchanged in 2 cases, but with an increase in $tcPO_2$ that allowed successful minor amputation [13].

Examples of Applications

(based on Japanese health insurance coverage and references 5 and 14 to 17)

Metabolic Disorders Familial hypercholesterolemia (FH) *** Lp(a) hyperlipoproteinemia [5] ***	Organ Transplant HLA-/ABO-incompatible kidney transplant * HLA-/ABO-incompatible liver transplant * Antibody-mediated rejection (AMR) *
Rheumatologic Disorders Systemic lupus erythematosus (SLE) * Malignant rheumatoid arthritis (MRA) *	Dermatologic Disorders Pemphigus * Pemphigoid * Toxic epidermal necrolysis (TEN) * Stevens-Johnson syndrome * Atopic dermatitis [14] **
Neurological Disorders Myasthenia gravis (MG) * Guillain-Barré syndrome (GBS) * Chronic inflammatory demyelinating polyneuropathy (CIDP) * Multiple sclerosis (MS) * Neuromyelitis optica (NMO) *	Renal Disorders ANCA-associated glomerulonephritis [15] * Anti-glomerular basement membrane disease [16] *
Hematologic Disorder Primary macroglobulinemia **	Others Peripheral arterial disease (PAD) **** Age-related macular degeneration (AMD) [17] **** Severe blood type incompatible pregnancy *
Hepatic Disorder Hepatitis C ***	

Recommended model

*: EC-30W, 20W, **: EC-40W, ***: EC-50W, ****: Rheofilter ER-4000 (refer to Rheofilter brochure)