AsahiKASEI

Cascadeflo™ EC

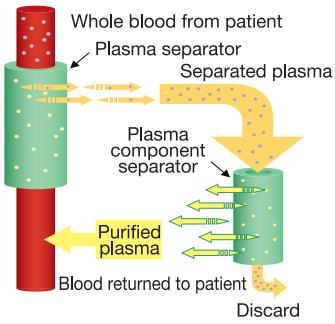
Asahi Plasma Component Separator
for Double Filtration Plasmapheresis (DFPP)

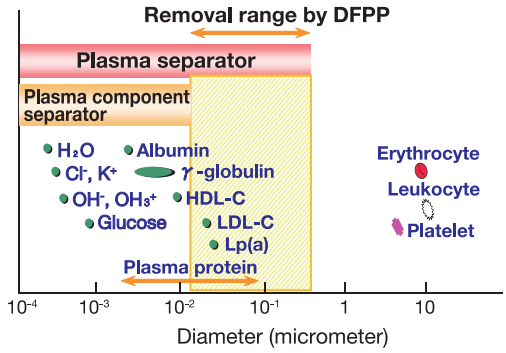
Minimal albumin loss & effective removal of target substances by selection of appropriate filter among the four different pore size models

ASAHI KASEI MEDICAL CO., LTD.
A Pioneer in Blood Purification

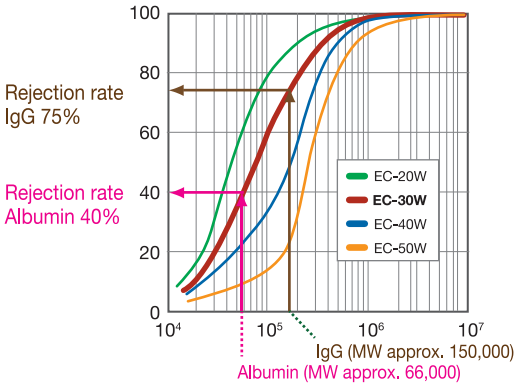
Separation Mechanism

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



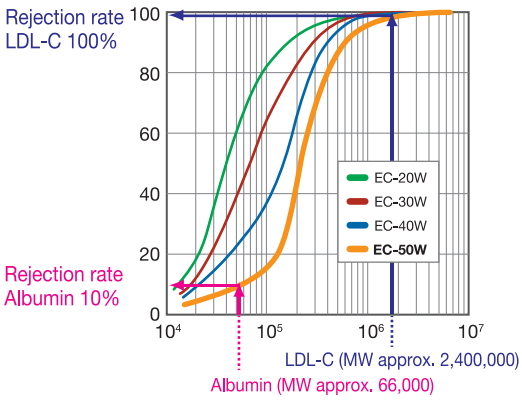
Use of EC-30W

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



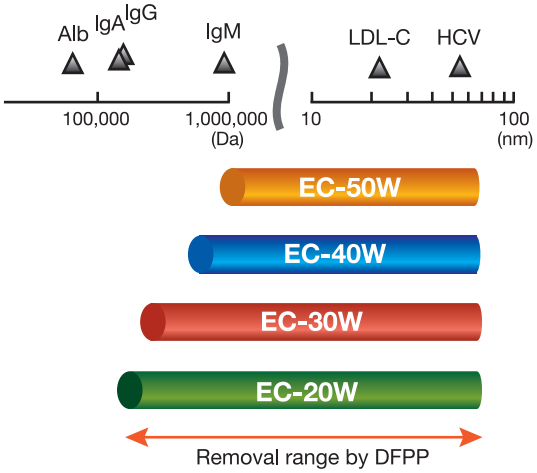
Use of EC-50W

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.

Indication

The Cascadeflo EC is designed for use in double filtration plasmapheresis (DFPP) to fractionate the plasma separated by the plasma separator into large-molecule-rich plasma and small-molecule-rich plasma.

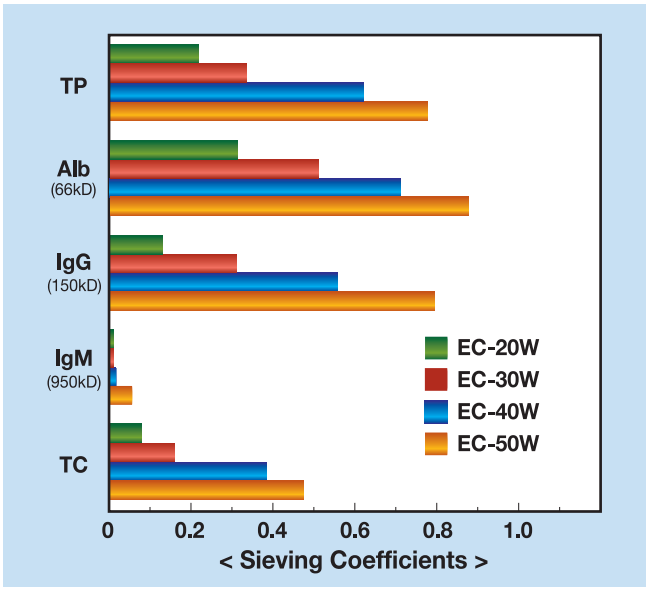
Features of Cascadeflo EC

- 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

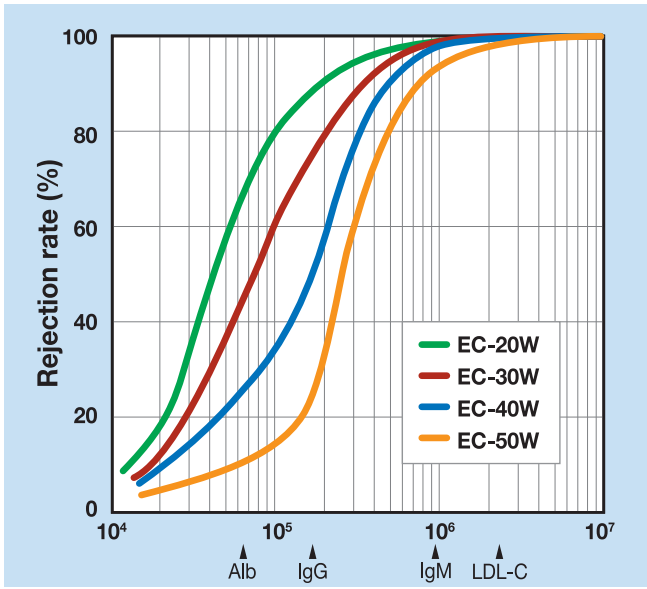
Sharp Cut-off Curve

Homogeneous distribution of pore size provides sharp cut-off feature

a) Permeability



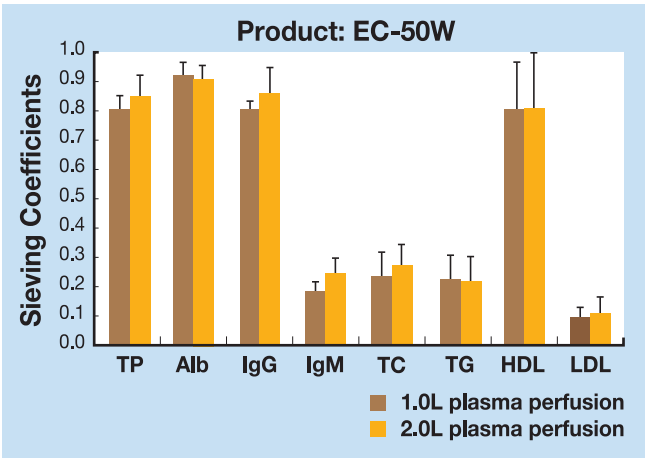
b) Cut-off Curve



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

Stable Sieving Coefficient

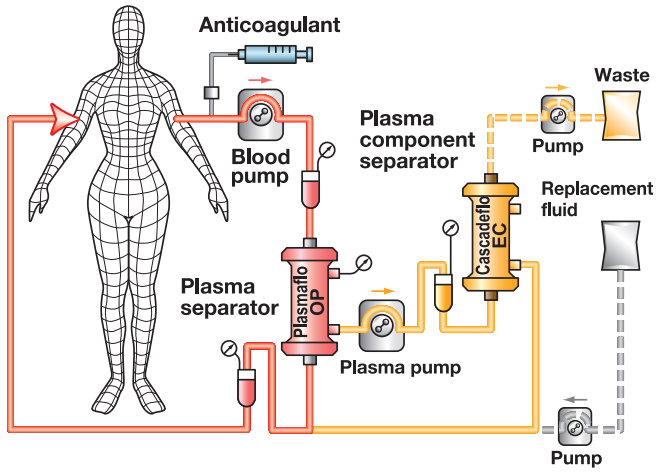
Unique microstructure of hollow fiber avoids clogging, and enables stable performance



***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 immunoadsoption) 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] ***

Rheumatologic Disorders
- Systemic lupus erythematosus (SLE) *
- Malignant rheumatoid arthritis (MRA) *

Neurological Disorders
- Myasthenia gravis (MG) *
- Guillain-Barré syndrome (GBS) *
- Chronic inflammatory demyelinating polyneuropathy (CIDP) *
- Multiple sclerosis (MS) *
- Neuromyelitis optica (NMO) *

Hematologic Disorder
- Primary macroglobulinemia **

Hepatic Disorder
- Hepatitis C ***

Organ Transplant
- HLA-/ABO-incompatible kidney transplant *
- HLA-/ABO-incompatible liver transplant *
- Antibody-mediated rejection (AMR) *

Dermatologic Disorders
- Pemphigus *
- Pemphigoid *
- Toxic epidermal necrolysis (TEN) *
- Stevens-Johnson syndrome *
- Atopic dermatitis [14] **

Renal Disorders
- ANCA-associated glomerulonephritis [15] *
- Anti-glomerular basement membrane disease [16] *

Others
- Peripheral arterial disease (PAD) ****
- Age-related macular degeneration (AMD) [17] ****
- Severe blood type incompatible pregnancy *

Recommended model

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

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

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