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Dextran sulfate sodium – DSS for colitis

Trade name: DSS

Chemical names: Dextran sulfate sodium salt, Dextran sulfate

Catalogue number: DB001

CAS nr: 9011-18-1

Structure:

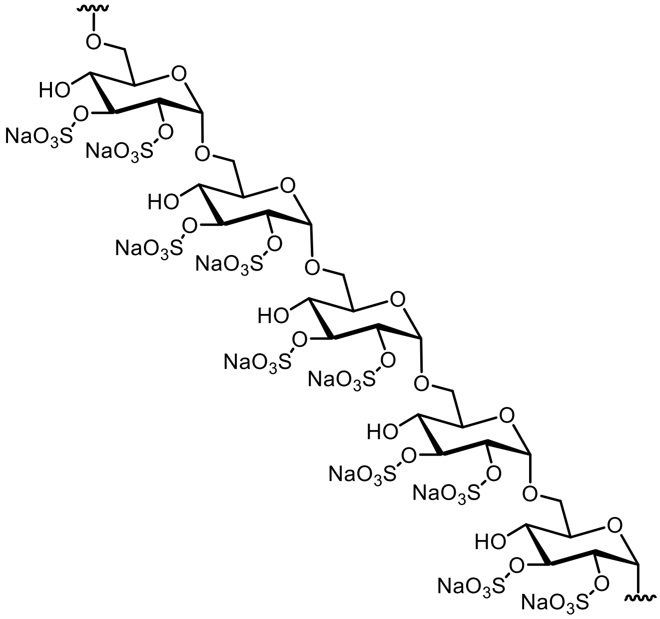

Fig.1. Structural representation of a fragment of dextran sulfate sodium (DSS). Dextran sulfate sodium for colitis has a mean molecular weight of 40 kDa and a sulfur substitution of 16-20 %.

What is DSS?

Dextran sulfate sodium abbreviated as DSS is sulfated derivative of a selected dextran fraction. After a program of studies on the various parameters that affect the induction of UC, it was concluded that a dextran fraction with mean molecular weight in the range 40-60 kD and a sulphur substitution of 16-20% gave optimal results.

DSS is a white powder which dissolves freely in water or salt solutions giving a clear solution. The product also dissolves in DMSO, formamide and certain other highly polar organic solvents but is insoluble in lower aliphatic alcohols, acetone, chloroform, dimethylformamide. The pH of an aqueous solution of DSS lies between 6.5 and 7.5. The solution contains a low percentage of phosphate as a stabilizer.

Physical and chemical properties

Molecular weight

The weight average molecular weight (Mw) of DSS lies within the range 35000-55000. A typical distribution is shown in Fig.2. It should be noted that the value for the Mw obtained by gel permeation chromatography (GPC) is a relative value as the column is calibrated with dextran fractions since no standard dextran sulfate fractions are available. Values obtained by light scattering measurements are somewhat lower.

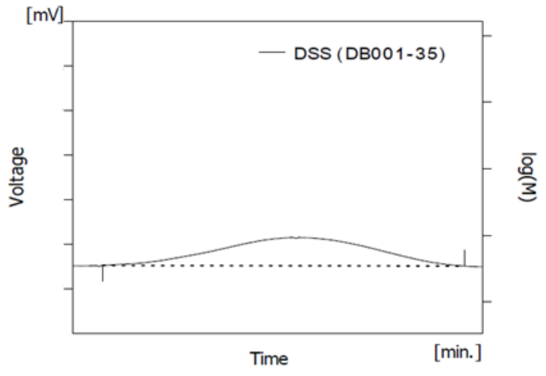

Fig.2 Distribution curve of DSS by GPC

The following factors may contribute to significant deviations in the values obtained by GPC.

1. Choice of column and eluent

2. Flow rate

3. Calibration procedures

4. Deviations in processing chromatograms.

It is therefore crucial that all these parameters be carefully controlled, and the calibration checked continuously against relevant standards.

Sulfation

The degree of sulfation of DSS is also a vital parameter in ensuring potency of the product and should lie between 16 to 20% sulfur.

Generally, this is determined by titration after exchange of the sodium ions. At these levels of substitution, each glucose unit in the dextran chain will contain at least two sulfate groups.

Storage and stability

The stability of dextran sulfate has been studied in both dry form and in solution. In dry form, a retrospective study showed that DSS is stable for more than five years when stored dry in well-sealed containers protected from light at room temperature. Opened containers should be sealed to prevent ingress of moisture.

To study the stability of DSS solutions in water. Solutions of 2.5% DSS were prepared and tested as follows:

1) 2.5% sterile, stored fridge 7 days.

2) 2.5% stored room temp. 11 days.

3) 2.5% stored room temp. 21 days

The results are summarized in Table 1 below.

Sample	Time (days)	pH	Free sulfate (mg/ml)	Mean mol. Wt.	Mw/Mn
1 (control)	7	6.54	0.03	42 000	1.4
2	11	6.25	0.03	41 400	1.4
3	21	5.50	0.03	41 900	1.4

Table 1. *Summary of stability data of dextran sulfate sodium (DSS). DSS was mixed with water to a final concentration of 2.5 %. All reported values are within the expected range. No degradation of DSS was seen during the 21-day study.*

All reported values lie within the expected range and did not provide any evidence of degradation of the DSS solution during the experimental interval studied (max. 21 days).

A prolonged storage (3 months) study of solutions of DSS at room temperature revealed a drop in pH and a slight release of sulfate groups (< 1% of the total). Sterilisation is preferentially performed by sterile filtration.

General notes on the application of DSS

Since its introduction by Okayasu and coworkers in 1987 (1) and subsequent extensive studies on experimentally induced colitis by L-G.Axelsson, A-C.Bylund-Fellenius, S.Ahlstedt and co-workers (2-6), several thousand publications have appeared. The following summary is based on random selection of publications up to 2012 and applications in mice, rats, and other experimental animals. A brief update has been included.

Experimental procedures

Generally, 2-7% solutions of DSS are prepared and filled into the drinking bottles. Although a small percentage of phosphate is added to the DSS during production to stabilize the pH, adjustment 6-7 may be achieved by adding dilute alkali. The solution when not used should be refrigerated. To conserve the amount of DSS used, it is advisable to only fill the bottle with the animals daily requirements. The liquid intake does not appear to be affected by the addition of DSS and free access to 2.5% or 5% DSS represents a daily intake of 3.7 g and 7.4 g per kg per day respectively. (2,p.208).

Dose studies reported by L-G.Axelsson (2) in Balb/c mice receiving 2.5% DSS for up to 35 days did not reveal any mortalities and no rectal bleeding was observed. However, areas of inflammatory activity and significant changes in colon length, spleen weight of feces were noted. At 5% DSS, there was a steady increase in the severity of the inflammation with a pathogenesis resembling human colitis. After day 7, rectal bleeding increased, colon length shortened, and fatalities were recorded. The colitis was most pronounced in the distal colon.

The induction of colitis may be followed by several sets of parameters notably, survival time, body weight, rectal bleeding, spleen weight, diarrhea, colon length and appearance of the intestinal tissue. The symptoms generally appear from 7-10 days. The effect of DSS intake has been related to the actual intake of the solution by the animals. Vowinkel and co-workers used calibrated drinking vessels for each animal and recorded daily drinking volumes (7). The animals were then grouped according to intake. For practical reasons this procedure is seldom adopted.

DSS in mice

The response to DSS may vary according to the mouse strain used; thus LPS-insensitive strains, C3H//HeJ and C3H/He, showed more severe colitis with inflammatory signs mostly in the proximal colon whereas with BALB/c and CBA/H mice, the inflammatory response was found largely in the distal colon (8). In a further study, mice from nine strains were studied and major differences in genetic susceptibility to DSS were demonstrated (9). The animals received 3.5% DSS in acidified drinking water for 5 days thereafter only water.

In Table 2, data from randomly selected references record the strain/breed of the mice used and the dose and duration in days. Doses have ranged from 1-5% DSS and the duration of treatment from 3 to 35 days. However, in the majority of cases, colitis symptoms appear after 5-7 days (10-35).

Strain	Dose	Reference
Swiss-Webster	(7)	10
TNF-alphaand	-	
TNF-alpha+	4.5% (7)	11
Balb/c	-	12
IL-6and IL-6+	4.5% (8)	13
C57BL/6	2.5%, (5)	14
Wild-type and Fat-1	2.5% (5)	15
Wild-type C57BL/6J(m)	3% (6)	16
C57BL/6 AhR null, WT	3.5% (7)	17
CBA/J(H-2k); BALB/c(H-2d) (f)	5% (7)	18
C57BL/6	5% (3-14)	19
Wild-type; DPIV -/-	2% (6)	20
Mice	3% (7)	21
WTC57BL/6; TR2 KO	3% (7)	22
Balb/c	1% (10)	23
WT C57BL/6(MFG-E8(+)	3.5% (7)	24
WT C57BL/6(IRF4 -/-)	3.5% (5)	25
BALB/c	5% (7)	26
C57BL/6J	3% (5)	27
WT; CCR9(-/-);CCL25(-/-)	2% (7)	28
WT eNOS+/+ and -/-	3%	29
BALB/c; NMRI/KI	2.5 – 5%	30
BALB/c; athymic nu/nu	-	
CD-1(BR)	5% (7-35)	31
IL-5-/and +/+	2.5%, 5% (9)	32
IL-4-/and +/+	-	33
C57BL/6	1.5% (7)	34
BALB/c	15% (10)	35

Table 2. Treatment of various mice strains with DSS.

DSS in rats

It has been found that rats generally required a somewhat higher concentration of DSS than mice for inducing experimental colitis. Many studies report the use of 5% DSS solutions. In

Table 3, data from selected references record the strain/breed of the rats used and the dose and duration of treatment (36-46).

Strain	Dose	*Reference*
Wistar	2% (2 weeks-6months)	36
Spraque-Dawley	5% (9)	37
Sprague-Dawley	5% (9)	38
Sprague-Dawley	5% (9)	39
Wistar(4-8week)	2-4% (7)	40
ACI	5 and 10% (14 or 102)	41
Wistar	2.5% (7)	42
Sprague-Dawley	5% (6)	43
Sprague-Dawley (30 day)	0.5-5% (7)	44
Wistar	5% (lowered to 3% (10)	45
Sprague-Dawley	5% (7)	46

Table 3. *treatment of various rat strains with DSS. The data comes from selected refeceres*

DSS in other animals

Table 4 lists some examples of the use of DSS in other animals.

Strain	Dose	Reference
Hamsters	1% (100)	47
Hamsters	2.5% (6); 3-5% (6)	48
Guinea pig	3% (4)	49
Guinea pig	-	50
Pigs (Yorkshire)	1.25 g/kg BW (5)	51
Pigs	-	52
Pigs	-	53
Pigs	-	54

Table 4. Treatment of other animals with DSS (47-54)

Some consideration should be made when adding other compounds to the DSS solution. DSS is a polyanion and the sulfate groups confer a considerable negative change to the molecule. Thus, addition of compounds with a cationic

character may lead to interactions with the DSS. Since the DSS model has been used to study various therapeutic approaches to the treatment of UC, it would be meaningful to take this into consideration. However, compounds such as sulphasalazine and 5-aminosalicylic acid have not been found to interact (3).

Literature update

Since this file was completed in 2013, interest in the DSS model for studying inflammatory bowel disease (IBD) has continued to grow. Annual statistics for publications involving the DSS model are listed below.

Year	No. of publications
2016	291*
2015	330
2014	270
2013	248
2017	406
2018	476

* Up to August

Most commonly, the model is used to study the mechanisms involved in the development of colitis and other IBDs and particularly the protective immune pathways and how they can be inhibited or stimulated. The therapeutic effects of various chemical agents and cell preparations have also been widely explored. The DSS model has also been valuable in conjunction with azoxymethane treatment or studying the genetic and environmental factors governing colitis associated carcinoma. (68)

Studies using this model have examined many mediators involved in systemic inflammation:

RAMP1, a protein that takes part in the terminal glycosylation, maturation, and presentation of the CGRP receptor to the cell surface (56)

Interleukins (IL-22, IL-23, IL23R, IL12RB1)

which play a vital role in inflammatory processes (55,62,63,66,70)

MMPs (Matrix metalloproteinase) MMP-3-an enzyme that hydrolyzes components of the extracellular matrix e.g., collagen and fibronectin. (64,72,73)

TNF- α; Tumor necrosis factor is a cytokine involved in systemic inflammation and is a member of a group of cytokines that all stimulate the acute phase reaction (71,74,75)

DOK-1 and DOK-2;. The DOK proteins present a docking platform for the compilation of multi molecular signaling complexes (66)

Remedial effects of stem cells and routes of delivery using the DSS model have been reported (58). Many studies have aimed at evaluating potential therapeutic agents for IBD (59,60,61,66,71,75,76).

The most frequently used strains of mice are C57BL/6, WT or Balb/c but often genetically modified variants have also been used. Doses often depend on the aim of the study and DSS concentrations of 1% are given for mild inflammation thereafter 2-5% for more severe manifestation).

Reviews

A search for reviews on the DSS model reveals 30 articles since 1987, many of which are directed on selected signaling and receptor processes.

Several reviews appear to be of a more general character (77-81).

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