SULFONAMIDE PHARMACEUTICAL COMPOSITION

FIELD OF THE INVENTION

[1] This invention relates to a sulfonamide pharmaceutical composition, and their preparation and use in the pharmaceutical industry.

BACKGROUND OF THE INVENTION

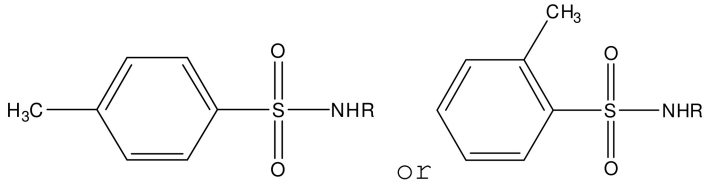
[2] Cancer is a common disease in the world today. Most cancers are diagnosed at late stage and the cure rate is low. Most of the current anticancer drugs have toxic side effects including hair loss, vomiting, decrease of white blood cell count, bone marrow suppression, and decrease in immune system function. The major reason is that these drugs act on part of the cell metabolic cycle, and they do not selectively target cancer cells as opposed to healthycells. When they kill cancer cells, they also damage healthycells, especially those healthycells that are undergoing rapid metabolism.

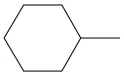
[3] Sulfonamide compounds have been clinicallyused as an antimicrobial for decades. Today,they arestill one of the most commonly used antimicrobials, second only to antibiotics because of theirbroad antibacterial spectrum, stability, ease of use, and low price. As more in-depth studies are conducted, researchers have found that sulfonamide compounds have a wider range of biological activities, including its diuretic effect, anti-thyroid effect, anti-diabetic effect, anti-hypoglycemic effect, and its ability to treat cataract. In recent years, a large number of sulfonamide compounds with anti-tumor activity have been reported, and many among them have entered clinical trials. These compounds act on different molecular targets and exhibit significant biological activity. Some compounds exhibit high selectivity and specificity for different targets.

[4] The mechanisms for the actions of these sulfonamide compounds are diverse, including disrupting tubulin polymerization, blocking normal cell cycle, inhibiting carbonic anhydrase, inhibiting folic acid dependent enzymes, inhibiting methionine aminopeptidase and histone deacetylase, and inhibiting vascular endothelial cell growth factor and so on.

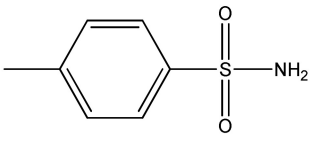
[5] Chinese Patent ZL97108988.4 disclosed the formulation and method to prepare injections of sulfonamide compounds.

[6] The compounds include:



Wherein R=H, C_2H_5, or .

[7] Preferably, sulfonamide compounds are selected from:



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[8] The formulation is as follows:

Said sulfonamide compound	10%~80%
PEG-400	10%~60%
1, 2-propanediol	5%~30%
Suberic acid	1%~20%
p-Toluenesulfonic acid	1%~15%
Dimethyl sulfoxide	0%~20%
Ethanol	0%~20%

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[9] When using the above formulation to prepare p-toluenesulfonamide injections, it was accidently discovered that the above formulation has low stability, tends to crystallize after

long storage time, and it also causes severe irritation to the injection site.

[10] Studies on the formulation and preparation method above showed that the problems are caused by suberic acid and p-toluenesulfonic acid. This invention effectively solved the problems by replacing suberic acid with sebacic acid, and replacing p-toluenesulfonic acid with 2-ethyl-1, 3-hexanediol.

DETAILED DESCRIPTION OF THE INVENTION

[11] The present invention solves the problems of low solubility and ease of crystallization associated with known injection formulations by improving the formulation and method to prepare injections of sulfonamide compounds. Comparative toxicity test also shows that the present formulation is less toxic and safer for clinical use.

[12] The goal of this invention is to provide an injection formulation comprising a sulfonamide compound, made with the following raw materials:

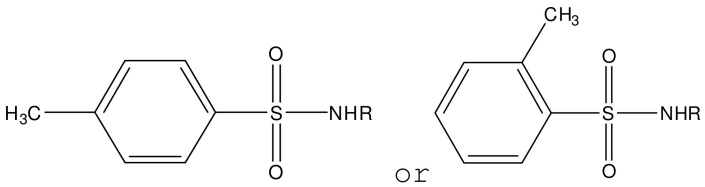
Raw Materials	Percentage by weight
Sulfonamide compound	20%-40%
PEG-400	20%-40%
1,2-propanediol	5%-10%
Sebacic acid	2%-5%
2-ethyl-1,3-hexanediol	10%-20%
Dimethyl sulfoxide	0-10%
Anhydrous ethanol	0-10%

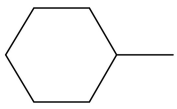
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[13] Among polyethylene glycol-400 (PEG-400), 1,2-propanediol, sebacic acid, 2-ethyl-1, 3-hexanediol, dimethyl sulfoxide and

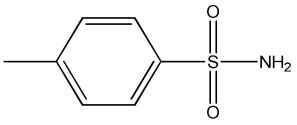
ethanol, only dimethyl sulfoxide and ethanol are dispensable, others are required.

[14] The sulfonamide compound is selected from one, or a mixture of two or more, at any ratio, of the following:



wherein R=H, C_2H_5, or .

[15] Preferably, the sulfonamide compound is selected from:



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[16] Preferably, the injection formulation of the present invention is prepared from the following raw materials:

Raw materials	Percentage by weight
P-Toluenesulfonamide	20-40%
PEG-400	20-40%
1,2-propanediol	5-10%
Sebacic acid	2-5%
2-ethyl-1,3-hexanediol	10-20%
Dimethyl sulfoxide	0-10%
Anhydrous ethanol	0-10%

[17] Further preferred, the injection formulation of this invention is prepared from the following raw materials:

Raw materials	Percentage by weight
p-Toluenesulfonamide	30%
PEG-400	30%
1,2-propanediol	8%
Sebacic acid	4%
2-ethyl-1,3-hexanediol	15%
Dimethyl sulfoxide	5%
Anhydrous ethanol	8%

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[18] The present invention improves upon the known injection formulations by removing suberic acid and adding the solubilizer 2-ethyl-1, 3-hexanediol. The combination of PEG-400, 2-ethyl-1, 3-hexanediol, and 1, 2-propanediol can decrease the amount of 1,2-propanediol in the injection formulation, thereby decreasing irritation at the injection site.

[19] Another goal of this invention is to provide a method to prepare the injection.

[20] The preparation of the injection of this invention comprises the following steps:

1) Putting a prescription amount of sulfonamide compound, PEG-400, and 2-ethyl-1, 3-hexanediolintoa container, stirring slowly at 85℃ -95℃ to form a miscible solution, Solution A, for later use;
2) Putting a prescription amount of sebacic acid and 1,2-propanediol, into a separate container, stirring slowly at 85℃ -95℃ to form a miscible solution, Solution B, for later use;
3) Mixing Solution A and Solution B while maintaining the temperature at 85℃-95℃, and stirring to obtain a homogenous solution for later use;

4) Putting a prescription amount of dimethyl sulfoxide and a small amount of anhydrous ethanolintoa container, stirring and mixingwell to obtain a homogenous solution,Solution C, for lateruse;

5) Cooling the mixture of Solution A and Solution B to 60℃, adding Solution C to the mixture, stirring and mixing well before cooling down to room temperature, adding the remaining amount of anhydrous ethanol and mixing well;

6) Filtering with 0.45um microporous membrane, aliquoting into 5ml ampoules and sealing the ampoules; and

7) Sterilizing at 121℃for 30 minutes.

[21] The beneficial effects of the present invention are further illustrated by the following experiments.

Table 1. Comparison of the formulation of the present invention with that disclosed in CN1073415C

The Present Invention		Example 2 in CN1073415C	
p-Toluenesulfonamide	30%	p-Toluenesulfonamide	30%
PEG-400	30%	PEG-400	33.5%
1,2-propanediol	8%	1,2-propanediol	16.4%
Sebacic acid	4%	Suberic acid	8.2%
2-ethyl-1,3-hexanediol	15%	p-Toluenesulfonic acid	3.7%
Dimethyl sulfoxide	5%	Dimethyl sulfoxide	6.7%
Anhydrous ethanol	8%	Ethanol	1.5%

[22] The present invention is an improvement on the basis of the prior art (CN1073415C). As shown in the above table, the formulation of the present invention made the following improvements as compared to the formulation disclosed in Example 2 of the Chinese patent CN1073415C:

1. Use of sebacic acid instead of suberic acid

2. Use of 2-ethyl-1, 3-hexanediol instead of p-toluenesulfonic acid

[23] By making the above improvements, this invention solved a range of issues associated with the known formulation such as low stability.

[24] The beneficial effects of the present invention are further illustrated by following studies.

[25] Experiment 1. Study on the Chinese Patent CN1073415C

[26] Comparative studies were conducted on injections prepared according to the examples disclosed in the CN1073415C patent.

Raw materials	Example 1	Example 2
p-Toluenesulfonamide	30%	40%
PEG-400	33.5%	40%
1,2-propanediol	16.4%	10%
Suberic acid	8.2%	3%
p-Toluenesulfonic acid	3.7%	2%
Dimethyl sulfoxide	6.7%	3%
Ethanol	1.5%	2%
Stability	Stored at 4℃±2℃ for 10 days, crystals precipitated	Stored at 4℃±2℃ for 10 days, crystals precipitated
LD50	12.54 mg/kg	11.30mg/kg

[27] Results show that crystals precipitated when the injection was refrigerated for a period of time, and this seriously affects the stability of the injection. After discovering the above problems, the inventors of this invention conducted research on the formulation and have found that the decrease in stability is likely to be caused by the presence of suberic acid and p-Toluenesulfonic acid in the formulation, for the following reasons:

The effect of PEG-400 in the formulation is as follows: acting as a water-soluble solvent to increase the compatibility of the injection with the tissues in the body.

The effect of 1, 2-propanediol in the formulation is as follow: acting as a water-soluble solvent, to increase the compatibility of the injection with the tissues in the body and inhibiting crystallization.

The effect of suberic acid in the formulation is as follows: it is a binary fatty acid and act as a fat-soluble solvent to increase the solubility of p-Toluenesulfonamide in the mixed solvent of the injection and to inhibit crystallization.

The effect of p-Toluenesulfonic acid in the formulation is as follows: it is an aromatic sulfonic acid compound, to increase the solubility of p-Toluenesulfonamide in the mixed solvent of the injection, and to inhibit crystallization.

The effect of dimethyl sulfoxide in the formulation is as follows: acting as an amphiphilic solvent to increase the solubility of p-Toluenesulfonamide in the mixed solvent of the injection, and to inhibit crystallization.

The effect of ethanol in the formulation is as follows: acting as an amphiphilic solvent to increase the solubility of p-Toluenesulfonamide in the mixed solvent of the injection, and to adjust the overall volume of the solution due to its good fluidity.

[28] The inventors conducted the following experiments to further validate the above conclusions:

The above problems still exist when the inventor adjusted the amount of other raw materials while keeping the amount of suberic acid and p-Toluenesulfonic acid constant.

Raw materials	Formula 1	Formula 2	Formula 3	Formula 4
p-Toluenesulfonamide	30%	40%	30%	40%
PEG-400	33.5%	40%	/	/
PEG-200	/	/	33.5%	40%
1,2-propanediol	16.4%	10%	/	/
Glycerin	/	/	16.4%	10%
Suberic acid	8.2%	3%	8.2%	3%
p-Toluenesulfonic acid	3.7%	2%	3.7%	2%
Dimethyl sulfoxide	6.7%	3%	/	/
Dimethylformamide	/	/	6.7%	3%
Anhydrous ethanol	1.5%	2%		
Water for injection	/	/	1.5%	2%
Stability	Stored at 4℃±2℃ for 10 days, crystals precipitated	Stored at 4℃±2℃ for 10 days, crystals precipitated	Stored at 4℃±2℃ for 10 days, crystals precipitated	Stored at 4℃±2℃ for 10 days, crystals precipitated

[29] The results show that the problem still exists when the formulation is adjusted while maintaining the same amount of suberic acid and p-Toluenesulfonic acid. We further confirmed that suberic acid and p-Toluenesulfonic acid is the cause of the stability problem.

[30] We then replaced suberic acid and p-toluenesulfonic acid.

[31] Experiment 2. Screening Experiment

[32] To replace suberic acid and p-Toluenesulfonic acid with a variety of substances while keeping other conditions unchanged, the screening process is as follows:

Screening Experiment

Raw materials	Formula A	Formula B	Formula C	Formula D	Formula E	Formula F
p-toluenesulfonamide	30%	40%	30%	40%	30%	40%
PEG-400	33.5%	40%	33.5%	40%	33.5%	40%
1,2-propanediol	16.4%	10%	16.4%	10%	16.4%	10%
Sebacic acid	/	/	8.2%	3%	/	/
Azelaic acid	/	/	/	/	8.2%	3%
Suberic acid	8.2%	3%	/	/	/	/
2-ethyl-1,3-hexanediol	/	/	/	/	3.7%	2%
Hexanediol	/	/	3.7%	2%	/	/
p-Toluenesulfonic acid	3.7%	2%	/	/	/	/
Dimethyl sulfoxide	6.7%	3%	6.7%	3%	6.7%	3%
Anhydrous ethanol	1.5%	2%	1.5%	2%	1.5%	2%
Stability	Stored at 4℃ ±2℃for 10 days, small crystals	Stored at 4℃ ±2℃for 10 days, small crystals	Stored at 4℃ ±2℃for 10 days, no precipitates	Stored at 4℃ ±2℃ for 10 days, no precipitates,	Stored at 4℃ ±2℃for 10 days, no precipitates,	Stored at 4℃ ±2℃for 10 days, no precipitates,

	precipitated	precipitated	, clear solution	clear solution	clear solution	clear solution

[33] The results show that the use of sebacic acid instead of suberic acid or the use of 2-ethyl-1,3-hexanediol instead of p-toluenesulfonic acid can solve the problems associated with the known method. However, as the dosage in the known formulation was unscientific, the preparation method involved an excessively long dissolving process, so the two formulations were combined and the amount of each raw material in the formula were determined.

[34] Experiment 3. Screening experiments for the amount of raw materials.

Raw Materials	Formula I	Formula II	Formula III	Formula IV	Formula V	Formula VI
p-Toluenesulfonamide	30%	40%	30%	25%	30%	40%
PEG-400	33.5%	40%	40%	35%	30%	30%
1,2-propanediol	16.4%	10%	5%	7%	8%	10%
Sebacic acid	2%	2%	5%	4%	4%	2%
2-ethyl-1,3-hexanediol	8%	3%	10%	15%	15%	18%
Dimethyl sulfoxide	6.7%	3%	5%	7%	5%	0
Anhydrous ethanol	1.5%	2%	5%	7%	8%	0
Dissolution time	8min	10min	4min	3min	5min	3.8min

[35] Results show that, although all raw materials dissolved in Formula I and II, the time taken is relatively long while for

Formula III-VI, raw materials dissolved faster and the final solution is clear and transparent.

[36] In addition, the present invention is further compared with existing pharmaceutical injections.

[37] Three samples were taken from each of Example 1, Example 5, Example6, and Example 7 (i.e., Formulation III-VI) of the present invention (Labelled as Samples A-D), and three samples were taken from self-prepared Example 2 from PatentCN1073415C (Labelled as Sample E). All samples were stored at 4℃±2℃ for 10 days and samples were observed at Day 0, Day 5, and Day 5 for crystal precipitation. Results are shown in Table 2:

Table 2: Comparison of crystal precipitation between Formulation III-VI of the present invention and CN1073415C Examples

Sample	0 Day	5 Day	10 Day
A1	Clear and transparent solution	Clear and transparent solution	Clear and transparent solution
A2	Clear and transparent solution	Clear and transparent solution	Clear and transparent solution
A3	Clear and transparent solution	Clear and transparent solution	Clear and transparent solution
B1	Clear and transparent solution	Clear and transparent solution	Clear and transparent solution
B2	Clear and transparent solution	Clear and transparent solution	Clear and transparent solution
B3	Clear and transparent solution	Clear and transparent solution	Clear and transparent solution
C1	Clear and transparent solution	Clear and transparent solution	Clear and transparent solution
C2	Clear and transparent solution	Clear and transparent solution	Clear and transparent solution

C3	Clear and transparent solution	Clear and transparent solution	Clear and transparent solution
D1	Clear and transparent solution	Clear and transparent solution	Clear and transparent solution
D2	Clear and transparent solution	Clear and transparent solution	Clear and transparent solution
D3	Clear and transparent solution	Clear and transparent solution	Clear and transparent solution
E1	Clear and transparent solution	Precipitation of fine crystals	Precipitation of crystals
E2	Clear and transparent solution	Precipitation of fine crystals	Precipitation of crystals
E3	Clear and transparent solution	Clear and transparent solution	Precipitation of fine crystals

[38] As shown in the above table, Formulations III-VI of the present invention showed a significant increase in stability at 4°C compared to self-prepared CN 1073415C Example 2. The solution is clear and transparent after 10-day storage, and no crystal precipitated.

[39] Accelerated Stability Experiment:

[40] Samples were taken from Example 1, Example 5, Example 6 and Example 7 (i.e., Formulation III-VI) of the present invention (Labelled as Samples A-D), and self-prepared CH1073415C Example 2 (Labelled as Sample E), and stored at 40 ℃± 2 ℃, 75% ± 5% RH. Relevant properties were assessed and results areshown in the below table:

Sample	Test items	Day 0	Month 1	Month 2	Month 3	Month 6

.A	Visible foreign matter		compliant	compliant	compliant	compliant	compliant
	Relevant Substance	Largest Single Impurity （%）	0.058	0.031	0.074	0.078	0.096
		Total impurities （%）	0.136	0.269	0.294	0.346	0.401
	Content		99.77	99.57	99.17	98.08	98.05
B	Visible foreign matter		compliant	compliant	compliant	compliant	compliant
	Relevant Substance	Largest single impurity （%）	0.058	0.078	0.079	0.086	0.097
		Total impurities （%）	0.136	0.155	0.217	0.263	0.415
	Content		99.77	99.61	99.56	98.70	98.57
C	Visible foreign matter		compliant	compliant	compliant	compliant	compliant
	Relevant Substance	Largest single impurity （%）	0.058	0.042	0.050	0.070	0.088
		Total impurities （%）	0.136	0.137	0.315	0.391	0.436
	Content		99.77	99.67	99.49	99.18	98.87
D	Visible foreign matter		compliant	compliant	compliant	compliant	compliant
	Relevant Substance	Largest single impurity （%）	0.058	0.046	0.074	0.082	0.085
		Total	0.136	0.253	0.319	0.326	0.421

		impurities (%)					
	Content		99.77	99.27	99.10	98.88	98.81
E	Visible foreign matter		compliant	compliant	compliant	compliant	compliant
	Relevant Substance	Largest single impurity (%)	0.058	0.067	0.119	0.131	0.168
		Total impurities (%)	0.136	0.253	0.571	0.644	0.850
	Content		99.77	99.46	99.06	98.59	97.36

[41] As shown in the table above, Formulations III-IV of the present invention were significantly more stable after storage at 40 ° C ± 2 ° C, 75% ± 5% RH for 6 months compared to CH1073415C Example 2. The growth rates of single largest impurity and total impurities were slower, and there were fewer impurities. The degradation rates of the raw materials were also slower and there was less degradation for Formulations III-IV.

EXAMPLES

[42] The following examples are included to further illustrate the present invention. It should not be regarded as a limitation on the present invention.

[43] Example 1: Injection

Raw materials	Percentage by weight
p-Toluenesulfonamide	30%
PEG-400	30%
1,2-propanediol	8%

Sebacic acid	4%
2-ethyl-1,3-hexanediol	15%
Dimethyl sulfoxide	5%
Anhydrous Ethanol	8%

[44] Preparation method:

1) Putting a prescription amount of sulfonamide compound, PEG-400, and 2-ethyl-1, 3-hexanediol into a container, stirring slowly at 85℃ -95℃ to form a miscible solution, Solution A, for later use;
2) Putting a prescription amount of sebacic acid and 1,2-propanediol, into a separate container, stirring slowly at 85℃ -95℃ to form a miscible solution, Solution B, for later use;
3) Mixing Solution A and Solution B while maintaining the temperature at 85℃ -95℃, and stirring to obtain a homogenous solution for later use;
4) Putting a prescription amount of dimethyl sulfoxide and a small amount of anhydrous ethanol into a container, stirring and mixing well to obtain a homogenous solution, Solution C, for later use;
5) Cooling the mixture of Solution A and Solution B to 60℃, adding Solution C to the mixture, stirring and mixing well before cooling down to room temperature, adding the remaining amount of anhydrous ethanol and mixing well;
6) Filtering with 0.45 um microporous membrane, aliquoting into 5 ml ampoules and sealing the ampoules; and
7) Sterilizing at 121℃ for 30 minutes.

[45] The purpose of adding anhydrous ethanol in this formulation is to control the total volume of the final solution, and further control the total drug content in the formulation. Therefore, the amount of anhydrous ethanol to be added in Step 4 should be slightly less than the prescription amount.

[46] Example 2. Comparative Safety Test

[47] Using mice as animal model, Example 1 of the p-toluenesulfonamide injection was compared with CN1073415C Example 2 by administering a single intravenous injection at the tail vein for comparative toxicity test. Results are shown below:

[48] Animal death rate is lower for Example 1. LD50 of CN 1073415C Example 2 is 11.30mg/kg, (95% CI = 9.47-13.13 mg/kg) LD50 of Example 1 of the present invention is 18.10 mg/kg (95% CI = 15.2-21.0 mg/kg). After the improvement of the current invention, i.e. replacing p-toluenesulfonic acid with 2-ethyl-1,3-hexanediol, LD50 of the drug was increased by 60% ($P < 0.01$), significantly reducing the toxicity of the injection.

[49] Example 3. Efficacy Experiment

[50] Example 1 of the present invention was tested on animals. Table 2 shows the effect of intramuscular injection of Example 1 on the development of lung cancer in mice.

Table 2 Effect of intramuscular injection of Example 1 on lung cancer development in mice

Group	Treatment	Dosage (/kg/d×10d)	No. of subjects		Body weight		Average weight of tumor (X±SD)(g)	Tumor-inhibiting rate (%)	P value*
			Start	End	Start	End			
1	NS(control)	2.0ml	11	11	20.7	27.9	3.52±0.62	0.0	>0.05
	Solvent (control)	2.0ml	11	11	20.5	25.1	2.91±0.58	17.3	<0.01
	CTX	18.0ml	11	11	20.8	25.0	1.82±0.41	48.3	<0.01
	Example 1	0.5ml	11	11	21.9	25.4	1.81±0.25	48.6	<0.01
	Example 1	1.0ml	11	11	21.3	25.2	1.46±0.74	58.5	<0.01
	Example 1	2.0ml	11	11	20.2	24.0	1.25±0.72	64.5	<0.01

2	NS(control)	2.0ml	11	11	20.4	27.7	2.49±0.58	0.0	>0.05
	Solvent (control)	2.0ml	11	11	21.5	28.9	2.69±0.56	-8.0	<0.01
	CTX	18.0ml	11	11	21.6	28.8	1.54±0.27	38.2	<0.01
	Example 1	0.5ml	11	11	21.9	25.6	2.15±0.87	13.7	<0.01
	Example 1	1.0ml	11	11	21.0	25.8	2.00±0.82	19.7	<0.01
	Example 1	2.0ml	11	11	21.6	25.6	1.59±0.64	36.1	<0.01
3	NS(control)	2.0ml	11	11	21.0	27.6	2.51±0.46	0.0	>0.01
	Solvent (control)	2.0ml	11	11	21.4	28.5	1.82±0.74	27.5	<0.01
	CTX	18.0ml	11	11	21.7	27.4	1.02±0.35	59.4	<0.01
	Example 1	0.5ml	11	11	21.8	25.9	1.67±0.95	33.5	<0.01
	Example 1	1.0ml	11	11	21.1	25.3	1.43±0.74	43.0	<0.01
	Example 1	2.0ml	11	11	20.3	25.6	1.02±0.57	59.4	<0.01

[51] The results of the experiments showed that:

1) At 0.5ml, 1.0 ml, 2 ml, and 2.0 ml/kg/d×l0d, Example 1 has different levels of anti-tumor effect on mice transplanted lung tumor. Anti-tumor effect increases as dosage increases.
2) At 2.0 ml/kg/d×l0d dosage, Example 1 has no anti-tumor effect on mice liver cancer and mice sarcoma S-180.
3) This demonstrates that the selected dosages of Example 1 have significant anti-tumor effect on mice lung cancer.
4) Injection of Example 1 has a high therapeutic index formice cancer.

[52] Example 4. Clinical Trials.

[53] Single-arm clinical trial of Example 1 injection (PTS injection) for local intra tumoral injection in patients with severe airway obstruction due to central type lung cancer.

[54] Clinical studies of PTS injection conducted by the Guangzhou Institute of Respiratory Diseases and 21 clinical research

institutes approved by the Ministry of Health reached the following conclusions:

[55] 89 patients were enrolled in the PTS clinical trial. Of these, 10 dropped out, 7 were excluded from analysis and used only for safety assessment (either because the subjects did not meet the inclusion criteria or the investigator had a violation of clinical protocols). A total of 72 patients were included in the efficacy analysis.

[56] Among the 72 subjects aged between 23-79, 59 were males and 13 were females. Subject statistics based on their lung cancer stage: 46 cases in IV phase, 22 cases in stage IIIb, 4 cases in stage IIIa. Subject statistics based on the location of tumor, 6 cases of airway, 28 cases of left main bronchus, 30 cases of right main bronchus, and 8 cases of right intermediate bronchus.

[57] Results on efficacy:

[58] 72 patients with central lung cancer after 2-4 weeks of treatment with PTS local target tumor injection:

[59] Major efficacy index: objective response rate of intraluminal target lesion—according to RECIST: based on CT assessment, the objective response rate was 68.08% within 7days from the last treatment, and 48.61% after 30 days from the exit period, respectively.

[60] Major efficacy index: objective response rate of intraluminal target lesion—according to WHO standard: based on CT assessment, the objective response rate of intraluminal target lesion was 77.78% within 7days from the last treatment, and 54.17% after30 days from the exit period.

[61] Major efficacy index: improvement rate on luminal tumor blockage, applying CT assessment , the improvement rate for obstruction due to luminal tumor is 70.45% within 7days from the last treatment, and 70.47% after30 days from the exit period.

[62] Clinical benefit index: Compared with the baseline, the pulmonary function index FEV1 showed statistically significant improvement within 7 days after the last administration, with a rate of improvement of 34.72% and 18.06% at 30 days after the exit period; the total re-expansion rate for patients with atelectasis across different lobes was 44.44% (20/45). Arranged by the location with a descending re-expansion rate is as follows: 50.00% for the right middle lobe, 43.75% for the left lung, 42.11% for the left lower lobe, 38.46% for the right lower lobe, 35.00% for the left tongue lobe, and 25.00% for the right upper lobe.

[63] Analysis of the overall efficacy showed that, the target lesions significantly shrink after intratumoral injection of PTS, with the objective response rate and luminal tumor obstructionism provement rate close to 70%; clinical benefit index FEV1 improved more than 30%, pulmonary re-expansion rate improved more than 40%. The indexes above directly showed that patients have reduced target lesions after PTS treatment, their airway obstruction improved, indicating that respiratory functions and life quality significantly improved after PTS treatment.

[64] Results on safeness:

[65] During the entire course of the clinical trial on the 89 subjects, none of them exhibited bone marrow suppression, gastrointestinal reactions or other commonly observed adverse reactions associated with systemic chemotherapy.

[66] During the entire course of the clinical trial, vital signs, physical examination, blood examination, blood biochemical examination, immunology examination and electrocardiogram were monitored and showed no statistically significant changes.

[67] This demonstrates that intratumoral injection of PTS had littlesystemic impact on the patients.

[68] Example 5. Injection

Raw materials	Percentage by weight
p-Toluenesulfonamide	40%
PEG-400	30%
1,2-propanediol	10%
Sebacic acid	2%
2-ethyl-1,3-hexanediol	18%

Same method of preparation as Example 1.

[69] Example 6. Injection

Raw materials	Percentage by weight
p-Toluenesulfonamide	30%
PEG-400	40%
1,2-propanediol	5%
Sebacic acid	5%
2-ethyl-1,3-hexanediol	10%
Dimethyl sulfoxide	5%
Anhydrous ethanol	5%

Same method of preparation as Example 1.

[70] Example 7. Injection

Raw materials	Percentage by weight
P-Toluenesulfonamide	25%
PEG-400	35%

1,2-propanediol	7%
Sebacic acid	4%
2-ethyl-1,3-hexanediol	15%
Dimethyl sulfoxide	7%
Anhydrous ethanol	7%

Same method of preparation as Example 1.

What is claimed is:

1. A sulfonamide pharmaceutical composition, comprising the following raw materials:

Raw materials	Percentage by weight
Benzenesulfonamide compound	20%-40%
PEG-400	20%-40%
1,2-propanediol	5%-10%
Sebacic acid	2%-5%
2-ethyl-1,3-hexanediol	10%-20%
Dimethyl sulfoxide	0-10%
Anhydrous ethanol	0-10%

wherein the sulfonamide pharmaceutical composition is prepared by a process comprising the steps of:

1) adding the benzenesulfonamide compound, PEG-400, and 2-ethyl-1, 3-hexanediol into a container, stirring slowly at 85℃-95℃ to form a miscible solution, Solution A, for later use;

2) adding sebacic acid and 1,2-propanediol into a separate container, stirring slowly at 85℃-95℃ to form a miscible solution, Solution B, for later use;

3) mixing Solution A and Solution B while maintaining the temperature at 85℃-95℃, and stirring to obtain a homogenous solution for later use;

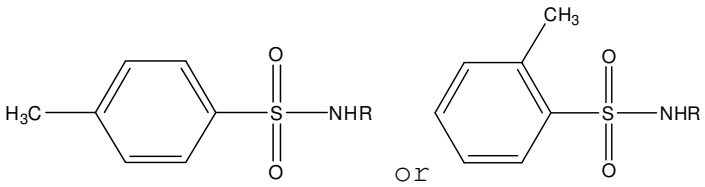
4) adding dimethyl sulfoxide and a small amount of anhydrous ethanol into a container, stirring and mixing well to obtain a homogenous solution, Solution C, for later use;

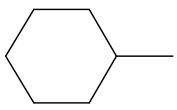
5) cooling the mixture of Solution A and Solution B to 60℃, adding Solution C to the mixture, stirring and mixing well before cooling down to room temperature, adding the remaining amount of anhydrous ethanol and mixing well;

6) filtering with 0.45 μm microporous membrane, aliquoting into 5 ml ampoules and sealing the ampoules; and

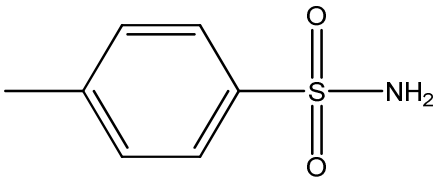
7) sterilizing at 121℃ for 30 minutes..

2. The sulfonamide pharmaceutical composition of claim 1, wherein the benzenesulfonamide compound is selected from one, or a mixture of two or more, at any ratio, of the following:



wherein R=H, C_2H_5, or .

3. The sulfonamide pharmaceutical composition of claim 1, wherein the benzenesulfonamide compound is:



.

4. The sulfonamide pharmaceutical composition of claim 1, wherein the benzensulfonamide compound is p-toluenesulfonamide.

5. The sulfonamide pharmaceutical composition of claim 1, wherein the sulfonamide pharmaceutical composition comprises the following raw materials:

Raw materials	Percentage by weight
p-Toluenesulfonamide	30%
PEG-400	30%
1,2-propanediol	8%
Sebacic acid	4%
2-ethyl-1,3-hexanediol	15%
Dimethyl sulfoxide	5%
Anhydrous ethanol	8%

.

6. The sulfonamide pharmaceutical composition of any one of claims 1-5, wherein said pharmaceutical composition is injectable.

7. A method to prepare said sulfonamide pharmaceutical composition of claim 1, comprising the steps of:

1) adding benzensulfonamide compound, PEG-400, and 2-ethyl-1, 3-hexanediol into a container, stirring slowly at 85℃ - 95℃ to form a miscible solution, Solution A, for later use;
2) adding sebacic acid and 1,2-propanediol, into a separate container, stirring slowly at 85℃ -95℃ to form a miscible solution, Solution B, for later use;
3) Mixing Solution A and Solution B while maintaining the temperature at 85℃ -95℃, and stirring to obtain a homogenous solution for later use;
4) adding dimethyl sulfoxide and a small amount of anhydrous ethanol into a container, stirring and mixing well to obtain a homogenous solution, Solution C, for later use;
5) Cooling the mixture of Solution A and Solution B to 60℃, adding Solution C to the mixture, stirring and mixing well before cooling down to room temperature, adding the remaining amount of anhydrous ethanol and mixing well;
6) Filtering with 0.45 um microporous membrane, aliquoting into 5 ml ampoules and sealing the ampoules; and
7) Sterilizing at 121℃for 30 minutes.

8. A method to prepare said sulfonamide pharmaceutical composition ofclaim 1, comprising the steps of:

Raw materials	Percentage by weight
p-Toluenesulfonamide	30%
PEG-400	30%
1,2-propanediol	8%

Sebacic acid	4%
2-ethyl-1,3-hexanediol	15%
Dimethyl sulfoxide	5%
Anhydrous ethanol	8%

1) adding p-toluenesulfonamide compound, PEG-400, and 2-ethyl-1, 3-hexanediol into a container, stirring slowly at 85℃ -95℃ to form a miscible solution, Solution A, for later use;
2) adding sebacic acid and 1,2-propanediol, into a separate container, stirring slowly at 85℃ -95℃ to form a miscible solution, Solution B, for later use;
3) Mixing Solution A and Solution B while maintaining the temperature at 85℃ -95℃, and stirring well to obtain a homogenous solution for later use;
4) adding dimethyl sulfoxide and a small amount of anhydrous ethanol into a container, stirring and mixing well to obtain a homogenous solution, Solution C, for later use;
5) Cooling the mixture of Solution A and Solution B to 60℃, adding Solution C to the mixture, stirring and mixing well before cooling down to room temperature, adding the remaining amount of anhydrous ethanol and mixing well;
6) Filtering with 0.45 um microporous membrane, aliquoting into 5 ml ampoules and sealing the ampoules; and
7) Sterilizing at 121℃ for 30 minutes.