Example 1 and Comparative Examples 1 and 2

In the following Example and Comparative Examples, a rubber sheet having an excellent gas permeability resistance of Compounding Example 2 in Table 3 was used. According to the compounding formulation, the mixture was kneaded using an open roll, aged for 24 hours and heated to obtain an unvulcanized rubber sheet. The resulting rubber sheet and D-1, D-2 and D-3 films with a thickness of 20 μm, obtained in the foregoing Reference Examples, were placed on a metallic mold for shaping, corresponding to a cross-sectional shape of a stopper shown in Fig. 3 (a), pressing at a mold-fastening pressure of 150 kg/cm^2 depending on the vulcanization conditions of at 150 to 180 °C, vulcanized for 10 minutes, and the whole body of the rubber stopper was laminated with PTFE or ETFE film to prepare a sealing stopper with a cross-sectional shape as shown in Fig. 3 (a). The size of the sealing stopper was allowed to correspond to that of an injection cylinder used in each test described hereinafter.

Measurement of Sliding Resistance Value

Injection cylinders each having a volume of 5 ml and 100 ml, made of plastic (polypropylene), and sealing stoppers having sizes shown in Table 5, corresponding to these injection cylinders were prepared and each of the sealing stoppers was thrusted and set into the injection cylinder. The sealing stopper was slowly thrusted therein in such a manner that the end of the sealing stopper reached a position for defining a specified volume, thus preparing a sample injection cylinder. Then, a commercially available disposable injection needle having a determined size was firmly inserted into the end of the sample injection cylinder. Using a commercially available syringe fitted with an injection needle, on the other hand, distilled water with the specified volume of the injection cylinder was charged in the end of the sample injection cylinder, during which care was taken so that air was not allowed to enter therein. The end of the injection cylinder was directed downwards, inserted in a metallic jig and the sealing stopper was thrusted into the end side at a rate of 100 mm/sec by a compression test disk of spherical seat type of a pressure senser-fitted measurement device [Autograph AG-1KND -commercial name- manufactured by Shimazu Seisakujo KK], during which a sliding resistance value was measured. The maximum value was read from the thus resulting sliding measured chart to define this as the sliding resistance value. In general, there was a tendency such that a value at the start of sliding, i.e. static friction resistance value Ffs was smaller than a value during sliding (kinematic frictionresistance value) Ffd. The results are shown in Table 5, from which it is evident that in Comparative Example 3 in which FTFE was laminated, the slidability is too low to measure the sliding resistance value and it is difficult to set in the injection cylinder.

Table 5

		Example 1	Comparative Example 2	3
Injection Cylinder Volume (ml)	Diameter of Sealing Stopper (mm)	PTFE Coated Sealing Stopper by Casting Method	PTFE Coated Sealing Stopper by Skiving Method	ETFE Coated Seal-Stopper by Extrusion Method
5	12.89	21.1 N*	20.4 N	not measurable
100	32.58	68.8 N	59.3 N	not measurable

(Note): * Newton (1 N = 9.8 kg)

Test for Estimation of Sealing Property for Long time

(Alternative Test for Estimation of Presence or Absence of Invasion of Microorganisms)

Using sealing stoppers of Example 1 and Comparative Examples 2 and 3 each having a size corresponding to an injection cylinder with a volume of 5 ml, the following procedure was carried out.

A plastic injection cylinder (volume 5 ml) having a cross-sectional shape shown in Fig. 1 (c) was washed and dried, followed by sealing the end thereof by a rubber cap. Water with a predetermined volume was then poured therein and each of the above described sealing stoppers was slowly inserted into the opening part. In the case of Comparative Example 2, the sealing stopper was forcedly thrusted therein. The whole weight (initial weight) of the sample cylinder was precisely weighed and then subjected to storage under an accelerating condition of a temperature of 40 °C and relative humidity of 75 % for at least 6 months, during which every one month, each sample injection cylinder was taken and the surface thereof was dried for 30 minutes in a desiccator, followed by precisely weighing each sample (at least five measurement points). The resulting data of weight change was treated in statistical manner to calculate as a regression function and a numerical value corresponding to three years is extrapolated in the time term to estimate and assess the sealing property for a long time after formulation of a medicament. In order to correspond to the real formulation, seventy samples were respectively prepared and investigated as to both plunger fitted- and plunger-free sealing stoppers.

A reduction curve Y for the time term X of each sample, $Y = -K + \alpha \ln X$, obtained by the above described statistical procedure can be represented in Example 1, as follows:

When fitting a plunger:

$$Y = -1.896 + 1.087 \times \ln X \qquad (a)$$

When not fitting a plunger:

$$Y = -4.200 + 1.594 \times \ln X \qquad (b)$$

When into the time term X of the above described regression function formulas (a) and (b) are extrapolated two years (17,520 hours) and three years (26,280 hours) to estimate weight reductions after two years and three years under normal state of water for injection in each sample, the weight reductions are 5.27 mg after two years and 5.71 mg after three years in the case of (a). The reduction ratios when the initial weight is 100 % are 0.11 % in two years and 0.11 % in three years. Similarly, the estimated values of the reduction and reduction ratio in the case of (b) are 6.31 mg and 0.12 % in two years and 6.96 mg and 0.13 % in three years.

The similar procedure to that of Example 1 was also carried out as to Comparative Example 1 (D-2) and Comparative Example 2 (D-3) to obtain reduction curves, and reductions and reduction ratios after two years and three years, obtained by extrapolation of the reduction curves. The results are shown in Table 6.

As shown in Table 6, the sealing property of the film (ETFE) of D-3 is more excellent, but the sealing stopper of Comparative Example 2 having this film laminated is inferior in slidability between the film and inner wall of the injection cylinder because of much higher sliding resistance so that it cannot be put to practical use. Even when using the same PTFE film, Example 1, in which the film by the casting method was laminated, is more excellent in slidable property and sealing property than Comparative Example 1, in which the film by the skiving method was laminated.

Table 6

Example	Laminated Resin (Reference Example) : Production Process	Plunger	Reduction Curve (Regression Function) $Y = -\alpha + K \cdot \ln X$	Reduction and Reduction Ratio After 2 Years	Reduction and Reduction Ratio After 3 Years
Example 1	PTFE (D-1)	yes	Y = -1.896 + 1.087 lnX	5.27 mg 0.11 %	5.71 mg 0.11 %
	: Casting Method	no	Y = -4.200 + 1.594 lnX	6.31 mg 0.12 %	6.96 mg 0.13 %
Comparative	PTFE (D-2)	yes	Y = -6.357 + 3.518 lnX	16.84 mg 0.32 %	17.79 mg 0.34 %
Example 1	: Skiving Method	no	Y = -6.676 + 3.617 lnX	17.17 mg 0.32 %	18.64 mg 0.35 %
Comparative	ETFE (D-3)	yes	Y = -7.379 + 2.683 lnX	10.31 mg 0.19 %	11.40 mg 0.22 %
Example 2	: Extrusion Method	no	Y = -7.214 + 2.658 lnX	10.31 mg 0.19 %	11.39 mg 0.21 %

Example 2

This Example was carried out as to a sealing stopper having an UHMWPE film laminated within the scope of the present invention, prepared by the extrusion method, and another sealing stopper having an UHMWPE film laminated (D-4) in an analogous manner to Example 1, Comparative Example 1 or 2, thus obtaining similar good results to Example 1.

From the foregoing tests, it could be confirmed that the present invention was very excellent in sealing property as well as slidable property.

Results of various tests effected as a sealing stopper for a syringe will be shown using the sealing stopper, as a typical example, of the type of Example 1 using the film of D-1.

Test for Liquid Sealing Property

(a) Dynamic Loading Conditions

Compressing Test according to Notification No. 442 of the Ministry of Health and Welfare, Standard of Device for Medical Treatment, "Standard of Disposal Injection Cylinder", December 28, 1970, and Bitish Standard.

Ten samples of clean plastic injection cylinders each having a specified volume were prepared, the end (lure part) of the injection cylinder being sealed by applying a rubber cap thereto. An aqueous Methylene Blue solution of 0.1 weight/volume % concentration in only a determined volume was poured in the injection cylinder. A rubber sealing stopper having a resin film laminated on the surface thereof according to the present invention or a comparative rubber stopper was slowly thrusted from the flange part of the injection cylinder and while turning up the head of the cylinder, the rubber cap was taken off at the lure part. A plastic plunger was screwed in a threaded part at the opening side of the sealing stopper and slowly pushed up upwards in such a manner that the liquid in the cylinder was not leaked, thus pushing out air in the end part of the cylinder. A rubber cap was again applied to the lure part and mounted on a measurement device for pressure test. After a pressure defined for medical treatment as shown in Table 7 was added for 10 seconds, the injection cylinder was taken off from the measurement device and an interface between the sealing stopper and injection cylinder was observed with magnifying ten times to confirm whether there was a leakage of the above described blue aqueous Methylene Blue solution through the interface part or not (Compressing Test①). The measured results are shown in Table 8, from which it is apparent that the sealing stopper of the present invention exhibits no leakage in any size of injection cylinders. In addition, Table 8 shows simultaneously the compressibility and sliding resistance of sealing stoppers, which teaches that even a sealing stopper having a larger compressibility (higher sealing property) has a higher sliding property.

When a further larger pressure was added to investigate presence or absence of leakage in addition to the above described defined Compressing Test (Compressing Test②), there was found no leakage as shown in Table 8.

Table 7

Application	Volume for Injection Cylinder	Pressure (10 sec.)
General Medical Treatment	less than 3 ml	4.0 kg/cm^2
	at least 3 ml less than 10 ml	3.5 kg/cm^2
	at least 10 ml less than 20 ml	3.0 kg/cm^2
	at least 20 ml less than 30 ml	2.5 kg/cm^2
	at least 30 ml	2.0 kg/cm^2
Very Small Amount	less than 2 ml	5.0 kg/cm^2
	at least 2 ml	4.0 kg/cm^2
Insulin	long	5.0 kg/cm^2
	short	4.0 kg/cm^2

Table 8

Injection Cylinder Volume (mm)	Injection Cylinder Inner Diameter (mm)	Sealing Stopper Outer Diameter (mm)	Compressibilty (%)	Sliding Resistance (N)	Compressing Test ①		Compressing Test ②	
					Pressure (kg/cm²)	Test Reselts (Obervation)	Pressure (kg/cm²)	Test Reselts (Obervation)
1	6.8	7.1	4.8	11.4	4.0	no leakage	6.9	no leakage
3	8.7	9.1	4.5	20.7	3.5	no leakage	5.9	no leakage
5	12.4	12.9	3.8	21.1	3.5	no leakage	3.7	no leakage
10	15.0	15.5	3.3	16.3	3.0	no leakage	3.5	no leakage
20	20.0	21.0	2.1	13.5	2.5	no leakage	3.5	no leakage
50	29.5	30.2	2.4	11.9	2.0	no leakage	2.6	no leakage
100	32.2	32.9	1.2	68.1	2.0	no leakage	2.5	no leakage

[note] Compressibility = [(Stopper Outer Diameter − Cylinder Inner Diameter)/Stopper Outer Diameter] × 100 %

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.

WHAT WILL YOU BUILD? | **sales@docketalarm.com** | **1-866-77-FASTCASE**

fastcase®
Smarter legal research.