Appeal decision

Appeal No. 2012-9689

Germany

Appellant PAT GMBH

Osaka, Japan

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The case of appeal against the examiner's decision of refusal for Japanese Patent application No. 2000-563262 entitled "PHOSPHATIDYLCHOLINE AS A MEDICAMENT FOR THE PROTECTION OF MUCOSA" [International Publication: February 17, 2000 as No. WO 2000-07577, National Publication: July 23, 2002 as National Publication of International Patent Application No. 2002-522381] has resulted in the following appeal decision:

Conclusion

The appeal of the case was groundless.

Reason

No. 1 History of the procedures

The application is an application with an international filing date of August 6, 1999 (priority claim under the Paris Convention based on August 6, 1998 (DE) Germany, December 15, 1998 (DE) Germany). In response to the notice of reasons for refusal dated December 2, 2009, a written argument and a written amendment were filed on May 25, 2010. In response to the final notice of reasons for refusal on September 7, 2010, a written argument and a written amendment were filed on May 25, 2010. In response to the final notice of reasons for refusal on September 7, 2010, a written argument and a written amendment were filed on March 8, 2011, but a decision to dismiss the amendment was made on January 16, 2012 and a decision of refusal was issued on the same date. In response, an appeal against the examiner's decision of refusal was made on May 24, 2012 together with a written amendment, and a written amendment (of formality) was submitted on October 15, 2012, and a written supplement was submitted on October 16, 2012. In response to the inquiry dated September 20, 2013, a response letter was submitted on December 24, 2013.

No. 2 Decision to dismiss the amendment submitted on May 24, 2012

[Conclusion of Decision to Dismiss Amendment]

The written amendment submitted on May 24, 2012 (hereinafter referred to as "The Amendment") shall be dismissed.

[Reason]

1. The Invention after amendment

The Amendment is to modify the following Claims 1 to 8 of the scope of the claims that had been amended by the written amendment on May 25, 2010, which was the subject of the decision of refusal:

"[Claim 1]

A medicament for the protection of mucosa in the colon, comprising an effective concentration for disease treatment of phosphatidylcholine as an active substance in a pH-dependent delayed release form.

[Claim 2]

The medicament of Claim 1 for the treatment of colon diseases or colitis.

[Claim 3]

The medicament of Claim 1 or 2 for oral application involved with pH-dependent delayed release of active substances in the lower ileum and colon.

[Claim 4]

The medicament of any one of Claims 1 to 3, wherein a pH-dependent delayed release formulation comprises a gastric acid-resistant cover shield and/or a carrier matrix.

[Claim 5]

The medicament of Claim 4, wherein the gastric acid-resistant cover shield comprises an acrylic polymer.

[Claim 6]

A use of phosphatidylcholine for the manufacture of a medicament in an oral or a rectal application form releasing an active substance with a pH-dependent delay in the lower ileum and colon, the medicament being intended for the treatment of colitis ulcerosa, pouchitis, and the other inflammatory bowel diseases (Crohn's disease, diversion colitis, infectious enteritis/colitis, or inflammation due to irradiation, antibiotics, chemotherapeutic agents, pharmacals or chemicals) or for the treatment or prophylaxis of colonic cancer.

[Claim 7]

The use of Claim 6, wherein the medicament is in a rectal application form for topical treatment of inflammation at the rectum or ileal pouch.

[Claim 8]

The use of Claim 6, wherein the medicament is in an oral application form, and the content of the active substance of a final formulation is 1 to 500 mg."

with the following claim set:

"[Claim 1]

A medicament comprising a therapeutic concentration of phosphatidylcholine as an active substance in a rectal application form for topical treatment of inflammation at the

rectum or ileal pouch or in an oral application form involved with delayed release of active substance in the lower ileum and colon for the treatment of colitis ulcerosa, pouchitis, colonic diseases, and the other inflammatory bowel diseases (Crohn's disease, diversion colitis, infectious enteritis/colitis, or inflammation due to irradiation, antibiotics, chemotherapeutic agents, or chemicals) or for the treatment or prophylaxis of colonic cancer.

[Claim 2]

The medicament of Claim 1, wherein said therapeutic concentration is at least 500 mg."

2. Propriety of amendment

(1) Claim 1

The Appellant argues that "Claim 1 after the Amendment is made by combining major constituent elements recited in Claims 1 to 7 before the Amendment."

In Claims 1 to 5 before the Amendment of the Invention of "medicament," Claim 1 before the Amendment is "a medicament for the protection of mucosa in the colon, comprising an effective concentration for disease treatment of phosphatidylcholine as an active substance in a pH-dependent delayed release form." Each of Claims 2 to 5 before the Amendment depends directly or indirectly from the Claim 1. On the other hand, Claims 6 to 8 before the Amendment are method inventions, and Claim 6 before the Amendment is "a use of phosphatidylcholine for the manufacture of a medicament in an oral or rectal application form releasing an active substance with a pH-dependent delay in the lower ileum and colon." Each of Claims 7 to 8 before the Amendment depends directly or indirectly from Claim 6.

In contrast, Claim 1 after the Amendment specifies the "form" of "medicament" as "rectal application form for topical treatment of inflammation at the rectum or ileal pouch" or "oral application form involved with delayed release of active substance in the lower ileum and colon." The matter specifying the Invention of Claim 1 before the Amendment that the "rectal application form" is "a pH-dependent delayed release form" is cancelled. The matter specifying the Invention of Claim 1 before the Amendment that the "oral application form" is "pH-dependent" is cancelled.

Accordingly, Claim 1 after the Amendment relates to "a form" of "phosphatidylcholine" in the invention according to medicament and encompasses a form other than "a pH-dependent delayed release form," which extends the scope of claims. Therefore, the Amendment does not correspond to one aiming at restriction of the scope of claims.

Further, the Amendment of the above Claim 1 is not for the purpose of the correction of a typographical error or clarification of an ambiguous statement.

Accordingly, the Amendment violates the provisions of Article 17-2(4) of the Patent Act before revision by the Act No. 24 of 2002, of which the provisions then in force shall remain applicable according to revision supplement Article 2(1) of the Act No. 24 of 2002. Therefore, the Amendment should be dismissed for the provision of Article 53(1) as applied mutatis mutandis by replacing certain terms pursuant to Article 159(1) of the Patent Act.

(2) Claim 2

Claim 2 after the Amendment is "the medicament of Claim 1, wherein said therapeutic concentration is at least 500 mg." This is rewritten in the form of an independent claim that does not depend from Claim 1 after the Amendment as in the following:

"A medicament comprising a therapeutic concentration of at least 500 mg of phosphatidylcholine as an active substance in a rectal application form for topical treatment of inflammation at the rectum or ileal pouch or in an oral application form involved with delayed release of active substance in the lower ileum and colon for the treatment of colitis ulcerosa, pouchitis, colonic diseases, and the other inflammatory bowel diseases (Crohn's disease, diversion colitis, infectious enteritis/colitis, or inflammation due to irradiation, antibiotics, chemotherapeutic agents, or chemicals) or for the treatment or prophylaxis of colonic cancer."

Here, regarding "therapeutic concentration," there is no description of "concentration" in the specification. Regarding "therapeutically effective amount," paragraph 0012 discloses that "the subject matter of the present invention is a medicament comprising a therapeutically effective amount of phosphatidylcholine sufficient to achieve mucosa protecting effects at the colon." Therefore, it is construed as the "amount" of phosphatidylcholine effective for the treatment of disease. The understanding is consistent with the description of "Menge" (Note by the body: a German expression having the meaning of "amount") in the specification of the international application of the case.

Examining the specification of the present application, however, it cannot be recognized that the original specification of the application discloses the amount of "at least 500 mg" without upper limit as "a therapeutic concentration" (or "content of active substance").

Additionally, the Appellant argued in the written amendment (of formality) on October 15, 2012 that "Claim 2 after the Amendment corresponds to Claim 8 before the Amendment and defines an amount of the active substance of formulation, which is supported by, for example, the description of paragraph 0012 in the original specification of the application." Therefore, just to be safe, the above argument is examined below.

Claim 8 before the Amendment specifies that "the use of Claim 6, wherein the medicament is in an oral application form, and a content of the active substance of a final formulation is from 1 to 500 mg." This is rewritten in the form of an independent claim that does not depend from Claim 6 before the Amendment as in the following:

"A use of phosphatidylcholine for the manufacture of a medicament comprising a content of an active substance of a final formulation of 1 to 500 mg in an oral application form releasing the active substance with a pH-dependent delay in the lower ileum and colon, the medicament being intended for the treatment of colitis ulcerosa, pouchitis and other inflammatory bowel diseases (Crohn's disease, diversion colitis, infectious enteritis/colitis, or inflammation due to irradiation, antibiotics, chemotherapeutic agents, pharmacals, or chemicals) or for the treatment or prophylaxis of colonic cancer."

Comparing Claim 2 after the Amendment with this, if "the content of active substance" should be construed as corresponding to "therapeutic concentration" as the Applicant argues, "1 to 500 mg" is modified to "at least 500 mg." It is obvious that the range is different.

Further, paragraph [0012] in the specification of the subject patent has the following description:

"The subject matter of the present invention is a medicament comprising a therapeutically effective amount of phosphatidylcholine sufficient to achieve mucosa protecting effects at the colon. The content of the active substance of final formulation is 1 to 500 mg, preferably 100 to 300 mg. Dosage forms suitable for oral application may include tablet, granule, capsule, pellet, or pellet tablets. Formulations may further include common pharmaceutical additives such as support or carrier substances. Formulations suitable mainly for rectal application include clysma, foam, ointment, gel, lotion, and suppository. These contain active substances in an amount of 10 mg to 10 g, preferably up to 5 g. According to the severity of diseases, the agents may be applied once or several times daily."

Specifically, what is described as "a content of the active substance" is "1 to 500 mg," "100 to 300 mg," "10 mg to 10 g," or "up to 5 g" only. The Appellant's argument that the definition of "at least 500 mg" without an upper limit is supported by the description of the paragraph 0012 is not acceptable.

Accordingly, the Amendment violates the provisions of Article 17-2(3) of the Patent Act before revision by the Act No. 24 of 2002, of which the provisions then in force shall remain applicable according to revision supplement Article 3(1) of Act No. 24 of 2002. Therefore, the Amendment should be dismissed for the provision of Article 53(1) as applied mutatis mutandis by replacing certain terms pursuant to Article 159(1) of the Patent Act.

No. 3 Regarding the invention

1. The Invention

The written amendment dated May 24, 2012 is to be dismissed as aforementioned. Therefore, the invention according to Claim 1 of the present application (hereinafter referred to as "The Invention") is specified by the matters recited in Claim 1 of the scope of the claims of the written amendment dated May 25, 2010 as in the following:

"A medicament for protection of mucosa in the colon, comprising an effective concentration of phosphatidylcholine for disease treatment as an active substance in a pH-dependent delayed release form."

2 Cited publication and its descriptions

(1) Publication 1 (Digestion, 1992, Vol. 53, No. 1-2, p. 35-44: Cited Document 1 in the examiner's decision) cited in reasons for refusal of the examiner's decision distributed before the priority date of the present application has the following descriptions: Additionally,the underlines are applied by the body.

(Publication 1-1) "Effects of phosphatidylcholine and phosphatidylinositol on acetic-acidinduced colitis in rats.

Abstract

The therapeutic effects of exogenous phosphatidylcholine and phosphatidylinositol on acetic acid-induced colitis in rats were evaluated. A uniform colitis developed 4 days after instillation of 4% acetic acid for 15 s in an excluded colonic segment, also resulting in a 6fold increase in mucosal permeability. Instillation of 12.5 mg phosphatidylcholine once daily from the day after acetic acid instillation and for the following 2 days partially prevented the development of colitis causing partial mucosal restoration. By increasing the phosphatidylcholine dose to 25 and 50 mg, a better preventive effect was achieved. By starting the phosphatidylcholine instillation immediately after the acetic acid exposure, almost complete prevention of the colitis could be obtained. Similarly, 50 mg phosphatidylinositol in each instillation with the first administration immediately after acetic acid administration resulted in complete prevention of the colitis and a significant decrease in mucosal permeability expressed as a plasma exudation into the colonic lumen. Similar results were obtained when phosphatidylcholine was administered immediately after acetic acid, but the drug then had to be applied twice daily. In contrast, a single application of the same total dose (150 mg) of the two different phospholipids, either 30 min before or immediately after acetic acid administration, could not prevent the development of colitis. It is concluded that both phosphatidylcholine and phosphatidylinositol have a therapeutic effect on the development of acetic acid-induced colitis in rats." (page 35, title and Abstract)

(Publication 1-2) "The optimal mode of treatment of colitis including ulcerative colitis remains to be found, although several studies have been performed in order to improve the therapeutic possibilities [1-5]. Phospholipids are the main constituent of surface-active materials and are of potential interest in the treatment of inflammatory bowel diseases. In previous studies we have demonstrated good prevention against peritoneal adhesions by intraperitoneal application of phospholipids [6]. Furthermore, extrinsic surface-active phospholipid and prostaglandin E2 analogues have been applied for gastric cytoprotection [7-9]. Prostaglandin E1 and E2 analogues have been used with good results in colonic mucosal protection in experimental colitis [3,10]. The cytoprotective effect of prostaglandins has been shown to be, at least partly, mediated by a localized increase in phospholipid concentration [8]. However, it remains to be proven whether extrinsic phospholipids alone may act cytoprotectively on colonic mucosa and, consequently, whether phospholipids may enhance the restoration of a colonic mucosal injury in colitis.

In a previous study we have shown that acetic acid in a dosage of 4% for 15 s administered into an excluded segment of the colon induced uniform colitis as evaluated on the 4th day after acetic acid instillation [11]. Furthermore the induced colitis showed some pathological similarities with human ulcerative colitis [11]. In the present study, we used the same model to evaluate the potential beneficial effects of two defined phospholipids, phosphatidylcholine (PC) and phosphatidylinositol (PI)." (page 36, left column)

(Publication 1-3) "Experimental Schedule

In all experiments, phospholipids were instilled into the excluded colonic segment in a volume of 5 ml through the upper colostomy aperture (the lower aperture was anchored for 1 min.) In the third and fourth experimental series, phospholipids were instilled at a volume of 2.5 ml. <u>The phospholipids were not washed out after instillation</u>." (page 36, right column, line 8 from the bottom to last line)

(Publication 1-4) "Results

Control Groups

In control colitis rats, the excluded colonic segment showed on the 4th day after

acetic acid instillation <u>pathological features of colitis</u> with mild-to-moderate signs of ulceration, inflammatory cell infiltration, crypt abscesses, dilated vessels, and edema, <u>and</u> the total morphological score was 14.7 ± 0.6 (fig. 1a). In contrast, control healthy rats had only mild edema and sometimes dilated vessels, and the total morphological score was 1.5 ± 0.2. Mucosal permeability increased from 0.24 ± 0.05 in control healthy rats to 1.43 ± 0.17 µl/min/g dry weight in the control colitis rats (p <0.001; table 1)." (page 37, right column, line 11 from the bottom to page 39, left column, line 5)

(Publication 1-5) "Effects of PC

Effect of Different Doses of PC. <u>PC induced dose-dependent restoration of the</u> <u>colonic mucosa</u> as evaluated the 4th day after acetic acid administration (table 1). Slight mucosal restoration was seen after treatment with PC at a dose level of 2.5 mg/ml for 3 days starting the day after colitis induction. However, when using this low dose, ulceration and active colitis were still evident and the total morphological score was 10.5 ± 0.6 . At a dose level of 5 mg/ml, the mucosa was better preserved than after 2.5 mg/ml, and the number of healing cysts was lower. At a dose level of 10 mg/ml, colonic mucosal restoration was evident with a clear reduction of ulceration. However, mucin hyposecretion, abscesses, submucosal edema, and infiltration of inflammatory cells were still seen, and the total morphological score was 8.3 ± 0.6 (fig. Ic). The dose-response relationship was highly significant (rs = 0.830, p<0.001; Spearman's rank correlation coefficient)." (page 39, left column, line 6 to right column, last line)

(Publication 1-6) "Effects of PC Administered at Different Time Points. Instillation of 10 mg/ml of PC immediately after acetic acid instillation and for 2 consecutive days improved the results as compared with those which could be seen when the treatment was initiated the day after acetic acid instillation (table 1). In fact, the colonic mucosa showed almost complete recovery on the 4th day after induction of colitis when PC treatment started immediately after acetic acid instillation (fig. 1d). However, mild inflammatory cell infiltration, cysts, mild edema, and vessel dilatation were still seen, and the total morphological score was 4.5 ± 0.4 . Initiating treatment immediately before acetic acid instillation and vessel dilatation starting the day after acetic acid instillation. By using the same dose of PC (10 mg/ml, for 3 days), but

dividing the daily dose into two administration times (2.5 ml twice daily) and starting the treatment immediately after acetic acid instillation, the results were further improved and complete mucosal restoration was achieved as evaluated 4 days after colitis induction with the total morphological score being 3.0 ± 0.4 (fig. le). Furthermore, mucosal permeability decreased significantly by this mode of treatment (PC 2.5 ml twice daily for 3 days), although it remained significantly higher than that in the control healthy rats.

The time-dependent response relationship was highly significant (rs=0.947, p<<0.001; Spearman's rank correlation coefficient)." (page 40, left column, line 1 to right column, line 13)

(Publication 1-7) "Effect of a Single Dose of PC. A single dose of PC of 150 mg (30 mg/ml, 5 ml) administered 30 min before colitis induction did not protect the mucosa from the development of colitis. In fact, 4 days after acetic acid administration, partly healed ulcers, inflammatory cysts, and mucin atrophy were seen, and the total morphological score was 11.0 ± 0.6 .

Furthermore, the same single dose of PC of 150 mg (30 mg/ml 5 ml) administered immediately after colitis induction had a slightly restorative effect on the mucosa. Despite signs of epithelial regeneration, active inflammation with inflammatory cysts, edema, and dilated vessels in the submucosa were still seen." (page 40, right column, line 14 to page 41, left column, line 7)

(Publication 1-8) "Fig. 1. Each photo is representative of changes in colonic muscosa within a group of 6 rats evaluated on the 4th day after operation and acetic acid instillation (except for control normal rats which received normal saline). HE. ×25.

a Control colitis rat; ulceration, disappearance of glands with mucous cell depletion, cyst formation, abscesses, moderate inflammatory cell infiltration, edema, and dilatation of vessels in the sub-mucosa are seen.

b Control normal rat; normal mucosa with absence of ulceration and inflammation, substantial mucin production within the glands, and slight edema in the submucosa are seen.

c Rat treated with PC of 10 mg/ml once daily for 3 days starting 1 day after colitis induction; mucosa without ulceration, but mucin hyposecretion, abscesses, inflammatory cell infiltration, and slight edema in the submucosa are seen.

d Rat treated with PC immediately once daily for 3 days; mucosa without ulceration, few cysts, mild inflammatory cell infiltration, and mild edema in the submucosa are seen.

e Rat treated with PC immediately twice daily for 3 days; well-preserved mucosa without ulceration, mild edema, and vessel dilatation in the submucosa are seen." (page 38)

(Publication 1-9) "Table 1. The protective effect of PC on acetic acid-induced colitis in the rat

Dose of PC	Administration schedule	Total dose of PC	Result	
			score	permeability
0 mg 0 mg	normal saline in control normal rats normal saline in control colitis rats	0 mg 0 mg	1.5±0.2* 14.7±0.6	0.24±0.05*** 1.43±0.17
2.5 mg/ml, 5 ml once daily for 3 days	start 1 day after acetic acid instillation	37.5 mg	10.5 ± 0.6^{a}	
5 mg/ml, 5 ml once daily for 3 days	start 1 day after acetic acid instillation	75.0 mg	9.3 ± 0.5^{a}	
10 mg/ml, 5 ml once daily for 3 days	start 1 day after acetic acid instillation	150.0 mg	8.3±0.6*,ª	
10 mg/ml, 5 ml once daily for 3 days	start immediately before acetic acid instillation	150.0 mg	8.7±0.4*,b	12 12
10 mg/ml, 5 ml once daily for 3 days	start immediately after acetic acid instillation	150.0 mg	4.5±0.4*,b	
10 mg/ml, 2.5 ml twice daily for 3 days	start immediately after acetic acid instillation	150.0 mg	3.0±0.4*,b	0.64±0.07***
30 mg/ml, 5 ml once	30 min before acetic acid instillation	150.0 mg	11.0±0.6	
30 mg/ml, 5 ml once	immediately after acetic acid instillation	150.0 mg	7.8±0.5*	

Table 1. The protective effect of PC on acetic acid-induced colitis in the rat

Each group included 6 rats for each dose level. Means \pm SEM are shown.

* p < 0.05, ** p < 0.01, *** p < 0.001, vs. control colitis.

^a PC dose-dependent group, correlation: n = 24, $r_S = 0.830$, p < 0.001.

Group treated with PC for 3 days with different timing, correlation: n = 24, $r_S = 0.947$, p < 0.001.

" (page 39, Table I.)

In Table 1, the score of colitis model showed a dose-dependent decrease in phosphatidylcholine (PC). Here, the morphological score and the mucosa permeability of control normal rats showed the minimum values, whereas those of control colitis model rats showed the maximum values. Thus, it can be seen from the data that therapeutic effects in the colitis model showed an increase in a dose-dependent manner on phosphatidylcholine (PC).

(Publication 1-10) "Discussion

A healthy colonic mucosa provides an efficient barrier between the potentially harmful environment and host integrity. This barrier is impaired in colitis, which in turn triggers the luminal immune system with a subsequent release of inflammatory mediators, including arachidonic acid, derived from phospholipids [12]. It has been shown that arachidonic acid metabolism is very similar in the acetic acid-induced colitis as compared with that seen in human inflammatory bowel disease [13]. This might imply that, although colitis can be triggered by a wide variety of stimuli, the same soluble proinflammatory factors mediate the final response [13]. Therefore, a high degree of similarity with regard to colonic morphology presumably exists regardless of the etiology of colitis. Moreover, other mechanisms known to be present in spontaneous human colitis, for example, increased mucosal permeability, altered vascularization, and reduced activity of mucosal enzymes (e. g. carboxypeptidase), have been reported to occur also in acetic-acid-induced experimental colitis [14-16]. An experimental model of colitis, such as acetic acid-induced colitis, could therefore be a useful tool for screening potentially therapeutic agents.

As previously shown [11] and also confirmed in the present study, acetic acid instilled in an excluded colonic segment at a dose level of 4% for 15 s induces uniform and reproducible colitis in the rat. This model shows some histopathological similarities with human ulcerative colitis and uniform features of the changes on the 4th day after acetic acid instillation. This time point was therefore selected for evaluating the effects of phospholipids in the present study. Furthermore, at this time point, colonic mucosal permeability (plasma exudation into the colon) increased 6-fold, which indicates a disruption of the protective barrier function of the colonic mucosa due to inflammation. This alteration in colonic permeability has been implicated in the pathogenesis of inflammatory bowel disease [17]. Thus, the measurement of permeability is an indicator of

mucosal impairment and inflammation.

A characteristic distribution of amphoteric surface-active phospholipids, chemically similar to pulmonary surfactant, exists on the colonic mucosa, similar to what is found in other parts of the gastrointestinal tract [18]." (page 42, left column, line 11 from the bottom to right column, last line)

(Publication 1-11) "Each of the major surfactant species identified is present on the luminal lining along the gastrointestinal tract in amounts exceeding by far those needed to provide a monomolecular layer [18]. The phospholipids have a hydrophobic (amphophilic) character with good ability of boundary lubrication. It has been reported that a hydrophobic lining of the luminal surface has a functional role and provides protection of the mucosal epithelium against chemical and mechanical injuries [18]. Observations that the intact mucosa behaves as being hydrophobic, whereas the ulcerated mucosa does not [18, 19], and that the well-known 'barrier breakers,' which dissolve or combine with phospholipids, remove this hydrophobicity [20], support these findings. Therefore, it is possible that the application of phospholipids, such as PC and PI, could either protect the mucosal barrier against breaking by toxic material or support an already compromised barrier by covering the injured mucosa and prevent the further development of the consequent cascade of immunological changes that otherwise would occur. In the present study, we found that both PC and PI, which are known to be highly surface-active membrane components [18, 21], have a clear therapeutic effect in acetic-acid-induced colitis in rats. This effect was dose dependent and an optimal effect was achieved by increasing the daily dose up to 50 mg (5 ml of 10 mg/ml). Furthermore, initiating phospholipid treatment immediately after acid instillation resulted in the best effect on mucosal preservation. This might imply that initiating treatment as early as possible after mucosal injury is important, probably because the phospholipids block the immunological cascade which develops after insulating the mucosal barrier. The same total dose of PC and PI divided into 2 daily doses resulted in an improved result as compared with the administration once daily of the same total dose." (page 43, left column, line 1 to last line)

(Publication 1-12) "These findings might be due to a longer contact period between the phospholipids and the colonic mucosa when the phospholipids were administered twice

daily. In line with this, we found that by using the same total dose of phospholipids which resulted in complete restoration of the mucosa when applied for 3 consecutive days, but administered in a single dose immediately after acetic acid instillation, only slight preservation on the mucosa could be achieved.

Thus, both kinds of phospholipids had therapeutic effects on acetic-acid-induced colitis in rats. Furthermore, the effect was optimized by starting the treatment as early as possible after colitis induction and by applying these agents repeatedly. In contrast, using the same total dose of phospholipids which induced complete recovery after acetic acid-induced colitis, but administered before acetic acid instillation, did not result in any beneficial, protective effect. This might imply that phospholipids affect the injured mucosa, but they have no effect on healthy colonic mucosa.

The two kinds of phospholipids had similar restorative effects on the mucosa in acetic acid-induced colitis. This effect might thus not be dependent on the composition of phospholipids but would rather be due to the adsorption of a monolayer from both phospholipids on the injured mucosa. The difference between the liposomal PC dispersion and the vesicle type of PI dispersion is due to the zwitterionic nature of PC contrary to the negatively charged PI. This difference is not seen in the mucosal restorative effect.

We conclude that both PC and PI have restorative effects on the mucosa in acetic acid-induced colitis in rats. The potential beneficial effect of colonic administration of phospholipids in human ulcerative colitis, however, requires further investigations in a clinical situation." (page 43, right column, line 1 to last line)

(2) International Publication No. WO 1997-28801 according to Publication 2 (Cited Document 2 in the examiner's decision) cited in reasons for refusal of the examiner's decision distributed before the priority date of the present application has the following descriptions: Additionally, the underlines are applied by the body.

(Publication 2-1) "<u>The present invention provides a therapeutic method of treating</u> inflammatory bowel disease (IBD) comprising locally administering to the rectum, colon, and/or terminal ileum of a patient in need of such treatment, an amount of nicotine effective to reduce the symptoms of IBD. In one embodiment of the present method, the nicotine is administered orally, by means of a unit dosage form that selectively releases nicotine in the terminal ileum and/or colon of the patient. In another embodiment of the method, the nicotine can be effectively administered to the colon by rectal administration of an enema formulation or rectal foam comprising nicotine. <u>Nicotine can also be delivered to the ileum or colon of an IBD patient by administration of an enterically coated unit dosage form</u>. The present invention also provides a novel composition particularly suitable for the colonic administration of nicotine comprising crosslinked polyacrylic acid polymers complexed with nicotine." (page 3, line 18 to page 4, line 1)

(Publication 2-2) "In a further preferred embodiment, nicotine is administered via oral ingestion. <u>The effective amount of nicotine can be locally administered to the colon of the patient by oral ingestion of a unit dosage form such as a pill, tablet, or capsule, comprising an effective amount of nicotine which is enterically coated so as to be released from the unit dosage form in the lower intestinal tract, e.g., in the ileum and in the colon of the patient. Enteric coatings remain intact in the stomach, but will dissolve and release the contents of the dosage form once it reaches the region where the pH is optimal for dissolution of the coating used. The purpose of an enteric coating is to substantially delay the release of the nicotine until it reaches its target site of action in the ileum or colon. Since nicotine locally administered to the colonic tissue in this fashion is only about 20% absorbed in the bloodstream (based on rectal administration), the systemic side-effects of nicotine can be avoided or minimized.</u>

Aqueous film-coating technology is employed for the enteric coating of pharmaceutical dosage forms. <u>Delayed-released oral nicotine dosage forms have the</u> potential advantage of delivering nearly all the nicotine to the ileum or colon in an easily administered form which can theoretically avoid the increased systemic rectal absorption seen with enemas. In addition, enterically coated nicotine will not have the dermatologic side effects directly related to patch delivery.

Thus, a useful enteric coating is one that remains intact in the low pH environment of the stomach, but is readily dissolved when the optimum dissolution pH of the particular coating is reached. This can vary between pH 3 to 7.5, depending upon the chemical composition of the enteric coating, but is preferably between about pH 6.8 and pH 7.2. The thickness of the coating will depend upon the solubility characteristics of the coating material and the site to be treated. The most extensively used polymer for enteric coating is cellulose acetate phthalate (CAP). However, CAP has an optimum dissolution pH greater than 6, and thus early drug release may occur. Another useful polymer is polyvinyl acetate phthalate (PVAP), which is less permeable to moisture and gastric fluid, more stable to hydrolysis, and able to dissolve at a lower pH, which could also result in early release of nicotine in the duodenum.

Another available polymer is hydroxypropyl methylcellulose phthalate. This has similar stability to PVAP and dissociates in the same pH range. Further examples of currently used polymers are those based on methacrylic acid, e.g. methacrylic acid ester copolymers with acidic ionizable groups, such as Eudragit L. S or LS and mixtures thereof, the choice dependent upon the site of required dissolution of the coating. Dosage forms coated with Eudragit, which dissolve in the ileum at about pH 6.8 and in the terminal ileum and caecum at about pH 7.2, have been developed for the delivery of 5-aminosalicylic acid, and can be used in accordance with the present invention." (page 7, line 1 to page 8, line 9)

(3) International Publication No. WO 1996-36319 according to Publication 3 (Cited Document 3 in the examiner's decision) cited in reasons for refusal of the examiner's decision distributed before the priority date of the present application has the following descriptions: Additionally, the underlines are applied by the body.

(Publication 3-1) "PHARMACEUTICAL DOSAGE FORM FOR COLONIC DELIVERY

TECHNICAL FIELD

The present invention relates to <u>novel spherical unit dosage forms to release</u> therapeutic agents at a point near the inlet to, or within the colon.

BACKGROUND OF THE INVENTION

Release of therapeutically active agents in the colon from a perorally administered dosage form is desirable in several situations, including: (1) topical treatment of diseases of the colon such as constipation, irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, carcinomas, and infection in which systemic absorption of the therapeutic agent is neither required nor desired; (2) systemic absorption of therapeutic agents such as peptides and proteins which are subject to lumenal degradation in the stomach and small intestine; and (3) systemic absorption of therapeutic agents for which peak systemic concentrations and pharmacological activity are desired at time significantly delayed from the time of peroral administration (i.e., peak plasma concentrations in the early morning just prior to arising, from a peroral dosage form ingested at bedtime). <u>Colonic release of therapeutically active agents from a perorally administered dosage form requires that release of said agent for topical activity or systemic absorption be prevented in the stomach and small intestine, <u>but permitted in the colon</u>. This in turn requires design of the dosage form to be such that it takes advantage of features of the gastrointestinal tract that indicate arrival of the dosage form in the colon, relative to other portions of the gastrointestinal tract (M. Ashford and J. T. Fell, J. Drug Targeting, 1994, 2:241-258). <u>Variable features include pH</u>, ionic strength, apparent velocity, and bacterial content <u>of the lumenal contents of the several anatomical portions of the gastrointestinal tract</u> as well as the residence time of a pharmaceutical unit dosage form therein (M. Ashford and J. T. Fell, J. Drug Targeting, 1994, 2:241-258; S. S. Davis, J. Contr. Rel., 1985, 2:27-38)." (page 1, lines 1 to 35)</u>

(Publication 3-2) "<u>The pH profile of the lumenal contents of the gastrointestinal tract has</u> <u>also been characterized and found to be relatively consistent</u> (D.F. Evans, G. Pye, R. Bramley, A. G. Clark, and T. J. Dyson, Gut, 1988, 29:1035-1041). The pH of the stomach may vary temporarily with prandial state, but is generally below about pH 2. The pH of the small intestine gradually increases from about 5 to 5.5 in the duodenal bulb to about 7.2 in the distal portions of the small intestine (ileum). The pH drops significantly at the ileocecal junction to about 6.3 and very gradually increases to about 7 in the left or descending colon.

A distinguishing feature of the colon relative to other portions of the gastrointestinal tract is the presence of exogenous bacteria. These are capable of enzymatically catalyzing reactions of which the host animal is incapable.

It has been recognized in general that dosage forms designed for colonic release may employ one of the following features to indicate arrival of the dosage form in the colon, relative to other portions of the gastrointestinal tract: (1) the generally increasing pH profile of the lumenal contents up to the ileocecal junction; (2) the relatively constant small intestinal transit time of a pharmaceutical unit dosage form (compensating for the highly variable stomach residence time); and (3) the presence of exogenous bacteria in the colon

(M. Ashford and J. T. Fell, J. Drug Targeting, 1994, 2:241-258).

Dosage forms employing the generally increasing pH profile of the lumenal contents of the gastrointestinal tract as a design feature to indicate colonic arrival typically employ film coatings of enteric polymers. These enteric polymers are polyanionic polymers which are insoluble in water and at low pHs, but begin to dissolve at pHs of about 5. Commercially available enteric polymers begin to dissolve within the pH range of about 5 to 7.

Examples of the use of this type of rationale to design dosage forms for delivery to the colon include: USP No. 5,171,580, issued Dec. 15, 1992, Boehringer Ingelheim Italia, which teaches a preparation for delivery in the large intestine and especially the colon, comprising an active containing core coated with three protection layers of coatings having different solubilities. The inner layer is Eudragit# S, with a coating thickness of about 40-120 microns, the intermediate coating layer is a swellable polymer with a coating thickness of about 40-120 microns, and the outer layer is cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinyl acetate phthalate, hydroxyethyl cellulose phthalate, cellulose acetate tetrahydrophthalate, or <u>Eudragit#L</u>.

<u>USP No. 4,910,021</u>, issued on March 20, 1990, Scherer Corp., teaches a targeted delivery system wherein the composition comprises a hard or soft gelatin capsule containing an active ingredient such as insulin and an absorption promoter. The capsule is <u>coated with a film forming composition being sufficiently soluble at a pH above 7</u> so as to be capable of permitting the erosion or dissolution of said capsule. <u>The film forming composition being sufficiently RS</u>, and Eudragit# S at <u>specific ratios to provide solubility above a pH of 7</u>. Coating levels above what is known in the art are not disclosed." (page 2, line 8 to page 3, line 18)

(Publication 3-3) "<u>The inventors have discovered that the amounts of enteric polymer</u> required to delay release of the therapeutic agent for a time approximately corresponding to the residence time in the small intestine can be determined by 1. knowledge of the dissolution behavior of the selected enteric polymer as a function of the size of the dosage form and <u>the pH</u> and velocity of an aqueous medium, and 2. an estimation of <u>the pH</u> and apparent velocity of the lumenal contents of the sequential anatomical segments of the small intestine and colon. <u>Since final dissolution of the enteric coating is desired to occur</u> in the colon, the enteric polymer comprising the coating of the unit dosage form must be selected and applied to the dosage form such that the coating will be soluble in the proximal portion of the colon, or at a maximum pH of about 6.3. As described below, the amounts of enteric polymer required to achieve the requisite delay in release of the therapeutic agent are greatly in excess of those revealed in the prior art." (page 6, lines 21 to 35)

3. Invention described in Publication 1

Publication 1 discloses in the item of "the effects of PC" that "<u>PC induced a dose-</u> <u>dependent restoration of the colonic mucosa</u>" (the point (Publication 1-5)). Therefore, it is obvious that PC is contained as an active substance, and an agent for mucosa in colon. Publication 1 discloses that "In the present study, we used the same model to evaluate the potential beneficial effects of two defined phospholipids, phosphatidylcholine (PC) and phosphatidylinositol (PI)." (Point (Publication 1-2)). Therefore, "PC" is "phosphatidylcholine."

Further, Publication 1 discloses "The cytoprotective effect of prostaglandins has been shown to be, at least partly, mediated by a localized increase in phospholipid concentration [8]. It remains to be proven, however, whether extrinsic phospholipids alone may act cytoprotectively on colonic mucosa and, consequently, whether phospholipids may enhance the restoration of a colonic mucosal injury in colitis." "In the present study, we used the same model to evaluate the potential beneficial effects of two defined phospholipids, phosphatidylcholine (PC) and phosphatidylinositol (PI)." (Point (Publication 1-2)). Thus the study of Publication 1 demonstrates the ability of phosphatidylcholine to cause the recovery from a colonic mucosal injury, which had not yet been demonstrated in the conventional technique. As a result, (Publication 1-11) and (Publication 1-12) demonstrate the mucosal protective effect and the restoration of damaged mucosa. Therefore, "the restoration of colonic mucosal injury" is seen as a result of "mucosa protection."

Further, "An agent for mucosa protection in colon" of the cited invention is the use of phosphatidylcholine in mucosa protection in the colon, which was evaluated by a model of uniform colitis induced by "applying acetic acid in a dosage of 4% for 15 s administered into an excluded segment of the colon" as described in (Publication 1-2), (Publication 1-4), and (Publication 1-5).

Further, as described in (Publication 1-5), (Publication 1-8), and (Publication 1-9), it was restored with a certain dosage concentration and amount. Therefore, Publication 1 also applies the concentration and the amount effective for colonic mucosal injury.

Consequently, Publication 1 discloses the following invention (hereinafter referred to as "the cited invention".):

"An agent for mucosa protection in the colon, comprising a concentration of phosphatidylcholine as an active substance effective for restoration of a colonic mucosal injury in colitis model."

4. Comparison

Regarding "a medicament for the protection of mucosa in the colon" of the Invention, the specification discloses, for example, that "The presented invention relates to medications containing as effective substrate phosphatidylcholine in an amount sufficient to treat diseases in which the mucosa-protective effect of phosphatidylcholine in the colon and terminal ileum (including pouch mucosa) is of advantage." (paragraph 0001), and that "The subject matter of the present invention is a medicament comprising a therapeutically effective amount of phosphatidylcholine sufficient to achieve the mucosa protecting effects at the colon." (paragraph 0012). Thus it is obviously pharmaceutical use based on the mucosa protecting effects of phosphatidylcholine on the colon.

Regarding "concentration effective for the treatment of disease" of the present invention, the specification fails to explain "concentration." Regarding "the therapeutically effective amount," there is a description in paragraph 0012 (See the above). This is construed as meaning "the amount" of phosphatidylcholine effective for the treatment of disease. The understanding is consistent with the description of "Menge" (The board's note: a German expression meaning "amount.")" in the specification of the International application.

Accordingly, the present invention and the cited invention have the following (Corresponding features) and (Different feature 1) to (Different feature 2):

(Corresponding features)

"An agent for mucosa protection in the colon, comprising phosphatidylcholine as an active substance."

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(The different feature 1)
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The present invention is "a medicament" comprising an effective concentration of phosphatidylcholine for disease treatment, whereas the cited invention fails to specify that.

(The different feature 2)

The present invention comprises phosphatidylcholine "in a pH-dependent delayed release form," whereas the cited invention fails to specify that.

5. Judgment

(1) Regarding the different feature 1

As is examined in the above "4. Comparison," "an agent for mucosa protection in the colon" of the cited invention is the use of phosphatidylcholine for mucosa protection in the colon, which was evaluated by a rat colitis model induced by acetic acid. In that model, colonic mucosal injury was restored with a certain dosage concentration and amount. Thus, it can be said that the effective concentration for the healing from colonic mucosal injury was applied.

Further, Publication 1 discloses that acetic acid-induced colitis of rat induced by "applying acetic acid in a dosage of 4% for 15 s administered into an excluded segment of the colon" was used as a model for evaluating <u>the potential beneficial effects</u> of phosphatidylcholine, wherein the colitis was "the uniform colitis" "showing some pathological similarities with human ulcerative colitis" in circumstances where "the optimal mode of treatment of colitis including ulcerative colitis remains to be found, although several studies have been performed in order to improve the therapeutic possibilities" (Point (Publication 1-2)). It also discloses that an experimental model of colitis, such as acetic acid-induced colitis, could therefore be a useful tool for screening potentially therapeutic agents (Point (Publication 1-10)). Therefore, a person skilled in the art would recognize that it was a model of human ulcerative colitis that provided a certain level of reliability.

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As a result, there is derived a conclusion, "we conclude that both PC and PI have restorative effects on the mucosa in acetic acid-induced colitis in rats. <u>The potential</u> <u>beneficial effect</u> of colonic administration of phospholipids in human ulcerative colitis, however, requires further investigations in a clinical situation." (Point (Publication 1-12)). Further, a person skilled in the art could understand from the aforementioned description that the consideration of working effect of phosphatidylcholine in Publication 1 was made on the premise that phosphatidylcholine was to be used for pharmaceuticals.

Further, Publication 1 confirms the restoration of mucosa in experimental colitis induced by acetic acid, a model having a plurality of mechanisms in common with naturally occurring human colitis (Point (Publication 1-10)). Therefore, a person skilled in the art who read the description of Publication 1 would expect that the administration of phosphatidylcholine to patients suffering from colonic diseases with mucosal injury might result in the restoration of mucosal injury to treat the colonic diseases.

Accordingly, beneficial effects for the treatment of patients having colonic diseases associated with mucosal injury are suggested, although the beneficial effects are required to be further investigated in a clinical situation. Thus, a person skilled in the art would have reasonably conceived of using phosphatidylcholine as a medicament.

Here, Publication 1 does not explicitly suggest "the effective concentration for disease treatment," but discloses that "PC induced dose-dependent restoration of the colonic mucosa" (Point (Publication 1-5)), which suggests the necessity of a certain level or more of the effective amount for treatment. In addition to "Effect of Different Doses of PC" (Point (Publication 1-5)), with regard to the effects of PC in each case of "Administered at Different Time Points" (Point (Publication 1-6)) and "Single Dose of PC" (Point (Publication 1-7)), mucosa protective effects are considered for different dosage amounts and dose frequencies (Point (Publication 1-9)).

Further, it is usual to apply an effective amount in the case of pharmaceuticals, and use any pharmaceutically acceptable carrier as well as active ingredient. Therefore, it is just in the ordinary course of business to contain them in a pharmaceutically acceptable formulation when using phosphatidylcholine according to the cited invention for treatment.

Additionally, Publication 1 also discloses phosphatidylcholine as "the drug" (Point (Publication 1-1)) and "these agents" (Point (Publication 1-12)). It can be said that the Invention only recognized such embodiments as "medicaments."

(2) Regarding the different feature 2

Regarding "pH-dependent delayed release form," the specification discloses: "For oral application, such medications are particularly suitable which release the effective substrate in a delayed fashion (retarded preparations). This retardation of effective substrate release is most usefully achieved by cover shields and/or carrier matrices which are gastric acid resistant and release the effective substrate in pH-dependent fashion into the lower ileum or colon." (paragraph 0009), and "For preparation of orally applied phosphatidylcholine, it is advantageous to use delayed released formulas to prevent absorption in the proximal small intestine. Phosphatidylcholine could be packed in high volume (e.g. 0.88 ml content) capsules (e.g. made of gelatin). Those can be covered with arylpolymers, e.g. the above mentioned Eugradit(R)-preparations. A combination of Eudragit(R)S and L-preparations (e.g. Eudragit(R)L/S 100) guaranties a delayed release at pH > 6.4, as it is present in the terminal ileum. The use of Eudragit(R) preparations and their mixture (L-, S-, and R-preparations) is established since a long time ago. In addition, it is possible that also other cover shield materials or application forms (also new developments) can be used for specific release of phosphatidylcholine in the terminal ileum if they are proven to provide the best solution to the problem." (paragraph 0010). It can be seen that there is a purpose to cause the orally applied phosphatidylcholine to act on the colon.

Publication 1 discloses the use of "an agent for mucosa protection in the colon" of the cited invention in an experimental condition of directly applying phosphatidylcholine to the colon (Point (Publication 1-3)).

On the other hand, it is well-known to a person skilled in the art to use an agent orally in a delayed release form that dissolves at a pH of the colon for delivery to the colon for improving colonic inflammation as described in Publications 2 and 3 (Point (Publication 2-2), (Publication 3-2), and (Publication 3-3)).

Consequently, a person skilled in the art could have easily conceived of making "an agent for mucosa protection in colon" of the Publication 1 invention in a pH-dependent delayed release form for the purpose of acting on the colon.

(3) Effect

The specification of the present application discloses in EXAMPLE 1 "Determination of MDR3-analogous proteins by MDR3-RNA in gastrointestinal tract using RT-PCR" (paragraph 0022), and in EXAMPLE 2 "Expression of MDR3 analogous proteins (RNA) in the ileoanal pouch epithelium" (paragraph 0030), and in EXAMPLE 3 "Expression of MDR3 analogous proteins (RNA) in terminal ileum of healthy subjects, and patients with Crohn's disease and ulcerative colitis" (paragraph 0031). The specification also suggests the relationship between phospholipid transporters of MDR3-related proteins and colitis ulcerosa (paragraphs 0013 to 0020); however, it fails to show any data that specifically confirm the effects of medicaments comprising phosphatidylcholine in a pHdependent delayed release form to "protect mucosa in the colon."

On the other hand, it is confirmed that "an agent for mucosa protection in the colon" of the cited invention may restore colonic mucosa, a colitis model, by phosphatidylcholine in a dosage-dependent manner as described in (Publication 1-5). The model is an in-vitro acetic acid-induced colitis excluded from a rat; however, the test method and the obtained results are specifically described (Points (Publication 1-3) to (Publication 1-9)). Thus the protective effects on colonic mucosa may be expected from the description of Publication 1. Further, pH-dependent delayed release form may have effects to deliver a necessary amount of phosphatidylcholine to the colon, which is expected from Publication 2 and Publication 3.

In view of the above, the effects of the Invention are expected from Publications 1 to 3.

(4) Appellant's allegation

Further, the Appellant argues in the written amendment (of formality) dated October 15, 2012 and the response letter dated December 24, 2013 that the animal model of Publication 1 is not an appropriate model, and in the response letter the Appellant argues about the description of Examples in the specification of the present application. Therefore, just to be safe, the argument is examined below:

Regarding the acetic acid-induced colitis model of Publication 1, the Appellant presents Evidence A Nos. 1 to 5 and argues that "several" and "similarity" of Publication 1

shows the insufficiency of the model of Publication 1, which is at most a model for acute inflammation of the distal colon, since Evidence A No. 1, a review published in 1995 with respect to an animal model of inflammatory colitis, did not refer to the model of Publication 1, and Evidence A No. 2 published in 2008 critically described the model of Publication 1. The Appellant also argues that the fixation of the colon is infeasible in humans.

Further, the Appellant argues that Evidence A Nos. 4 and 5 published in 2010 whose first authors are the inventor of the present application respectively disclose that the effective dosage amount of rPC in the treatment of chronic active colitis ulcerosa is 1 to 4 g daily, and rPC is the first treatment option for UC patients, and when the dosage amount for rat of Publication 1 is converted into human by use of Table 1 of Evidence A No. 3 published in 2005, it amounts to an unnecessarily high dosage amount compared to an ideal dosage amount found in Evidence A No. 4.

First of all, however, the Invention is "a medicament for the protection of mucosa in the colon, comprising an effective concentration of phosphatidylcholine for the treatment of disease as an active substance in a pH-dependent delayed release form." Thus, the Invention does not exclude acute condition from "disease," nor does it specify "effective concentration." Therefore, none of the above argument is based on the Invention, and thus the argument is not acceptable.

Even if these were specified, Publication 1 discloses the beneficial effect on the treatment of patients with colonic diseases associated with mucosa injury as a promising one as shown in the above "5. Judgment," while "Further investigations are required in a clinical situation." It cannot be seen from the description of Evidence A Nos. 1 to 5 that a person skilled in the art recognized a model of Publication 1 as an improper model as of the priority date of the present application. Further, Evidence A No. 2, which critically describes the acetic acid-induced colitis model, was published in 2008, much later than the present application.

Further, the experimental model is just a model for experiment, not a clinical test. Thus, even if the injection of phosphatidylcholine to the colon and the fixation of the colon after the injection, which was practiced in Publication 1, are infeasible to carry out completely the same method for human, it cannot be concluded that the experimental model is improper.

Regarding the example of the specification of the present application, the Appellant

argues that "the examples of the specification of the present application show that an insufficient amount of phosphatidylcholine in the intestinal lumen may cause IBD," "Accordingly, the examples of the specification of the present application obviously show that IBD patients have an insufficient amount or an activity of MDR3 proteins and show no secretion or insufficient secretion of phosphatidylcholine in the intestinal lumen, and that the administration of phosphatidylcholine to these patients may lead to the treatment or the protection of the colonic lumen."

As is discussed in the above "5. Judgment (3) Effect," Examples (EXAMPLES 1 to 3) relate to the expression of MDR3 analogous proteins. None of them uses phosphatidylcholine, nor do any confirm the "insufficient amount" of phosphatidylcholine (paragraphs 0022 to 0032). It cannot be seen from any other parts of the specification of the present application that "the administration of phosphatidylcholine to these patients may lead to the treatment or the protection of the colonic lumen," while it shows the relationship between phospholipid transporters of MDR3-related proteins and colitis ulcerosa (paragraphs 0013 to 0020).

Accordingly, none of the above Appellant's argument is acceptable.

(5) Regarding a draft amendment

Further, the Appellant presented a draft amendment in the response letter dated December 24, 2013. Examining just to be safe, the draft amendment incorporates the matters specifying the Invention of "a rectal application form for topical treatment of inflammation at the rectum or ileal pouch," which was not present in any of Claims 1 to 5 before the Amendment; i.e., the inventions according to "medicament" (Claims 1 to 5 amended by the written amendment dated May 25, 2010). Thus, the draft amendment extends the scope of claims.

Even if the above draft amendment were accepted, "a rectal application form" is a common method to deliver an active ingredient to the colon (Point (Publication 2-1)). Therefore, this point may not involve the inventive step. Further, EXAMPLE 3 of the specification of the present application has a description that negates the association of loss of phospholipids secretion in patients having "Crohn's diseases" with the diseases (paragraphs 0031 and 0032). Thus, there are deficiencies in the scope of the claims.

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6. Closing

As described above, the Invention was easily conceivable by a skilled person in the art on the basis of the descriptions of Publications 1 to 3, and thus it cannot be granted a patent in accordance with the provisions of Article 29(2) of the Patent Act.

Accordingly, the present application should be rejected without making a determination of the inventions according to the other remaining claims.

Therefore, the appeal decision shall be made as described in the conclusion.

June 11, 2014

Chief administrative judge: MURAKAMI, Kimitaka

Administrative judge: ANDO, Michiyo

Administrative judge: FUCHINO, Ruka