NALSAR PROXIMATE EDUCATION
NALSAR UNIVERSITY OF LAW, HYDERABAD
P.G.DIPLOMA IN PATENTS LAW
2004-05

Paper II - Practical

(Exploitation of Patents – Drafting, Specification & Patent Writing)

Time: 2 ½ hours. **Full marks: 60**

You are required to attempt either A or B (any one).

A)

You are required to draft an US patent application for Sara of Elgin, Illinois who has approached you with the following data and information.

Sara believes that she has an invention which pertains a cosmetic holder is a band made of cloth, such as elastic, with a plurality of loops sized for holding and securing the cosmetic items such that a user may quickly locate, remove from the holder, use, and return to the holder a desired cosmetic item. The size of the loops is dependent on which cosmetic items are to be stored and organized. The cosmetic items ideally include a cap and a body, and the loops are sized for securing the cap. The cosmetic holder may include a covering that covers the lateral portions of the band and may cover the portion of the loops through which the cosmetic item extends to permit insertion of the cosmetic items to a proper extent. The surface or covering of the cosmetic holder may include information or aesthetic decoration. A clip may be included for securing the cosmetic holder.

In accordance with the proposed invention, a cosmetic holder including a band with at least two loops sized for cosmetic items and securing the cosmetic items within the cosmetic holder is disclosed. The cosmetic holder may be comprised of cloth, and preferably elastic cloth where the cosmetic items are secured such that a user may simply remove or insert the cosmetic items, and where the cosmetic items otherwise remain secured. The loops may be sized for different sized cosmetic items. The cosmetic items ideally include a cap and a body, and the loops are sized for securing the cap.

The cosmetic holder may include a covering, and the covering may cover the lateral portions of the band and may cover the portion of the loops through which the cosmetic item extends. In such an embodiment, the cosmetic items may be inserted into the loops of the cosmetic holder, and the covering may permit insertion of the cosmetic items to a proper extent. The covering may be of a variety of materials, such as cloth or leather.

The cosmetic holder may include information on the surface of the cosmetic holder. The information may include identifying information of the cosmetic item secured therein, identifying information as to source or origin of the cosmetic holder, or identifying information as to source or origin of the cosmetic item. The cosmetic holder may include aesthetic decoration on the surface of the cosmetic holder. The cosmetic holder may include a clip for securing the cosmetic holder.

Additionally, in combination with cosmetic items where one of the cosmetic items includes a cap and a body, a cosmetic holder including an elastic band with at least two loops, the loops sized for cosmetic items and securing cosmetic items within the cosmetic holder, the cosmetic items being secured such that a user may simply remove or insert the cosmetic items but the cosmetic items otherwise remain secured, the loops being sized for securing said cap, is disclosed. The cosmetic holder of the combination may include a covering that covers the lateral portions of the band and covers the portion of the loops through which the cosmetic item extends, where the cosmetic items are inserted into the loops of the cosmetic holder, and where the covering permits insertion of the cosmetic items such that the cap is secured and the body may be easily removed for using the cosmetic item. The cosmetic holder of the combination may include information on the surface of the cosmetic holder. The cosmetic holder of the combination may include aesthetic decoration on the surface of the cosmetic holder.

The following figures exemplifies the proposed invention –

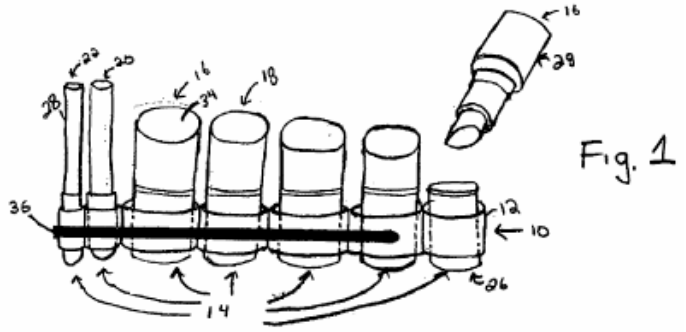

Fig. 1

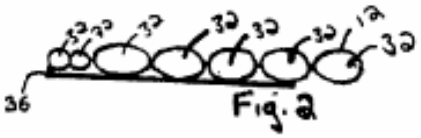

Fig. 2

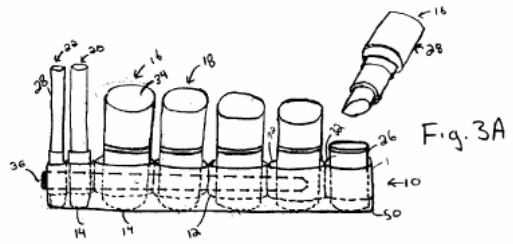

Fig. 3A

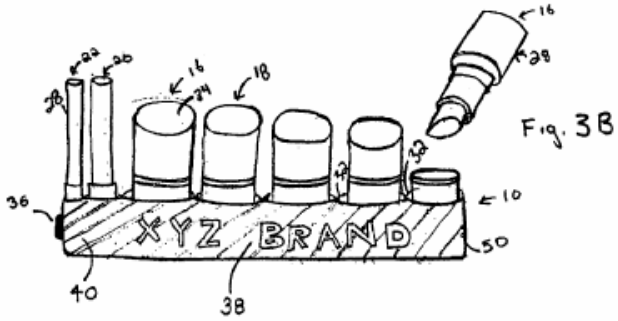

Fig. 3B

Cosmetics come in all shapes and sizes, and are ubiquitous in the lives of many people including stage performers, field news reports, and many of ordinary women. Often times, cosmetics are applied in situations where the person is unable to devote their full attention to applying the cosmetic, or makeup. For instance, a news reporter in a vehicle rushing to the site of a new story may be applying makeup while looking out the window watching the action of the story unfold. Another instance is when a woman is putting on lipstick as she drives to work. Still another instance is when a stage performer has marred their makeup while coming off stage, and the makeup must be re-touched (corrected) before going back on stage in a short period of time.

In the event the person desiring to put on makeup is unable to devote their full attention to locating and applying the cosmetic item, each of the cosmetics ideally is located easily. As is the more common case, a purse or makeup bag will contain a number of lipsticks, eyeliners, lip-glosses, lip-balms, and other cosmetic items. The person who is, for instance, operating a motor vehicle and is simultaneously searching for a lipstick in a purse will oftentimes grab the first one that is found in a bag, examine it, determine it is not the desired lipstick, put it back, and reach for another until finding the desired lipstick (or other cosmetic item). Oftentimes, the cosmetic items are strewn about within a woman's pocketbook or purse, along with a variety of other things carried in the purse. The other items in the purse make it more difficult to find the desired, loose cosmetic, as well as the loose cosmetics make finding the other items in a purse or pocketbook more difficult to quickly locate without requiring a great share of a person's attention.

Referring to FIG. 1, a first embodiment of a cosmetic holder 10 of the present invention is depicted. The cosmetic holder 10 secures a plurality of cosmetic items 14. The cosmetic holder 10 comprises a band 12 with a generally one-piece construction made of elastic or another type of cloth whereby the cosmetic items 14 may be secured as to allow the deliberate insertion or removal of the cosmetic item 14 from the cosmetic holder 10 while retarding or preventing the accidental removal of the item 14.

The band 12 is formed so as to have a plurality of loops 32, each loop sized for the cosmetic items 14 (see FIG. 2). At least two loops 32 are provided as a minimum, while a maximum is determined primarily by the utility to a user based upon the size of the cosmetic holder 10 and number of cosmetics items 14 carried. Generally, the band 12 would include from three to seven loops as it is believed this is the range of number of items the most common user would carry. As depicted, the cosmetic items 14 may be lipstick 16, lip-gloss 18, lip-liner 20, and eyeliner 22. This list is meant to be exemplary and non-exclusive, as other cosmetic items may be secured (such as mascara).

The loops 32 are appropriately sized for the various cosmetic items 14. Generally, lipsticks 16, for instance, are within a narrow range of diametrical size. Lip-liner 20 and eyeliner 22 are also, generally, within a narrow range of diametrical size. The preferred material for the loops 32 is elastic cloth so that the slight variance in size of cosmetic items of a particular type is rendered generally irrelevant.

The ideal cosmetics items 14 for the cosmetic holder 10 are cosmetic items 14 with a two-piece body construction comprised of a cap 26 and a body 28 wherein the body 28 contains the makeup to be applied, and the cap 26 protects the makeup from physical or environmental damage. The cosmetic item 14 is inserted into a loop 32 such that the cap 26 is secured in the loop 32. In this manner, the body 28 may be removed for using and applying the cosmetic while the cap 26 remains secure.
The contents or makeup of cosmetic items 14 are identifiable by the exterior of the cosmetic item 14. The body 28 of a lipstick 16 has a bottom end 34 to which a label or identifying insignia is affixed. The body 28 of a lip-liner 20 or an eyeliner 22 has a band of color on its exterior designating both what the item 14 is (i.e., eyeliner 22) and what color the item 14 is.

In use, the holder 10 has a plurality of cosmetic items 14 secured therein as inserted by the user of the holder 10. When a user desires a particular item 14, the entire holder 10 and the items 14 may be located easily in a purse or pocketbook, and the holder 10 organizes the items 14. A user may glance at the items 14 in the array as secured so as to scan across the identifying information of the items 14. This allows a user to avoid fumbling through a purse or makeup bag for a particular item 14. Instead, the user is able to quickly locate by feel all desired makeup items 14 without looking away from, for example, a roadway upon which the user is driving. Then, the items 14 may be held up for selecting the desired item 14, often with a quick glance. The body 28 of the desired item 14 then may be removed from the cap 26 and holder 10, while the cap 26 remains secure. Once the makeup or cosmetic has been applied, the body 28 may be returned to the holder 10 and cap 26.

In an embodiment of the present invention depicted in FIGS. 3A and 3B, the cosmetic holder 10 may include an outer covering 50. The covering 50 is a generally cloth material that is attached to the loops 32 of the holder 10. Alternatively, the covering 50 may be leather or another material. The covering 50 covers the lateral portions and the bottom of the band 12, the bottom of the band being the portion through which the cap 26 of the cosmetic items 14 extends. The covering 50 provides a utility and an aesthetic to the holder 10. The utility of the covering 50 is that the covering 50 is designed so that a cap 26 of a cosmetic item 14 is not pushed through the loop 32 entirely, thereby preserving the ability of the body 28 to be easily removed. The aesthetic of the covering 50 is that covering 50 may by decorated with a design 40 (such as tie-dyed, or plaid, or colors) or a logo, such as a brand or trade name 38.

Furthermore, the aesthetic appeal and style of the cosmetic holder 10 may be enhanced or based upon the covering 50 or the band 12. Different holders 10 could be made for different seasons and decorated as such. In addition, the holders 10 could be made for different styles, such as a holder 10 for more formal events which require formal wear and items with similar cachet, or a holder 10 for other casual events, such as a baseball game or outing. The loops 32 and band 12 of the holder 10 could be decorated, or the covering 50 could be decorated.

The loops 32 may include a window (not shown) into which identifying information may be inserted. Alternatively, other means may be provided on the loops 32 for identifying information, or the means may be provided on the covering 50. The covering 50, if provided, or the loops 32 may also provide space for or be used for a design, identifying information of the makeup or the manufacturer, a logo, or a fashion designer's name.

It should be noted that certain changes could be made to the cosmetic holder 10. For example, a clip 36 could be added for securing the holder 10 to a particular portion of a purse or makeup bag. The arrangement of the loops 32 need not be in a line as is depicted in the FIGS. 1, 2, 3A, and 3B, instead being any other different arrangement, such as being in two rows, or in an arrangement whose configuration of loops 32 for eyeliner 22 or lipstick 16 are differently configured.

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B)

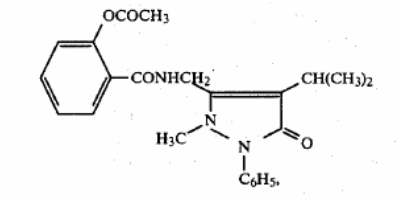
A research laboratory has approached you with the following data – draft a patent application to be filed with the USPTO.

The proposed invention relates to aspirin-isopropylantipyrine (N-3'a-propylphenazonyl-2-acetoxybenzamide), a compound that has yet to be found in known literature, a process for producing same, and its utilization as an analgetic, antipyretic and anti-inflammatory agent.

We previously found that the toxicity of isopropylantipyrine, a pyrazolone-type antipyretic and analgetic preparation, could be reduced and its stability could be enhanced without diminishing its antipyretic and analgetic activities by introducing a substituent to the 3-methyl group of isopropylantipyrine.

Our further researches led to the discovery that by introducing the acetylsalicylamide group to the 3-position methyl group there is produced a novel compound not found in prior literature, and that this compound can be synthesized in good yield by a simple procedure.

It was also found that this novel compound that can be expressed by the foregoing formula (I),

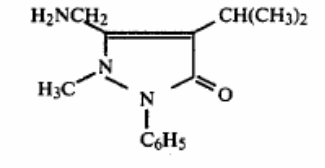


Formula I

while possessing superior analgetic, antipyretic and anti-inflammatory activity, demonstrates a marked reduction of such activities as cause gastric disorders that are possessed by aspirin and the side effects of the pyrazolone-type antipyretic and analgetic preparations. Moreover, it is not hygroscopic. It is hence a unique compound possessing good stability.

An object of this invention is therefore to provide a compound of the foregoing formula (I). Another object is to provide a process for producing the compound of formula (I), as well as methods of its utilization.

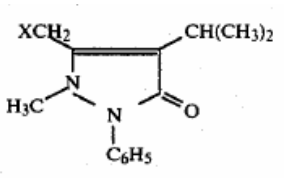
The aspirin-isopropylantipyrine of formula (I) of this invention can be prepared by reacting 1-phenyl-2-methyl-3-aminomethyl-4-isopropylpyrazolone of the formula II



Formula II

with either acetylsalicylic acid or a reactive acid derivative thereof.

The formula (II) compound can be obtained by reacting the compound of the formula (III)



Formula III

wherein X is halogen, with hexamethylenetetramine followed by hydrolysis of the product and thereafter reacting the product with ammonia. Examples of the halogen atoms of X in the foregoing formula (III) are, for example, Cl, Br and I.

The reaction between the formula (III) compound and hexamethylenetetramine can be carried out preferably in an inert solvent, for example in chloroform, at elevated temperatures, preferably at the reflux temperature. The reaction mole ratio can be suitably chosen. For example, the hexamethylenetetramine can be used in an amount of about 1.0 moles to about 1.2 moles per mole of the compound of formula (III).

After having reacted the hexamethylenetetramine with the formula (III) compound in the manner described hereinabove, the reaction product is hydrolyzed. The hydrolysis is preferably carried out by the acid hydrolysis technique. Acids that can be used include such mineral acids as hydrochloric acid. The hydrolysis can be carried out in an aqueous medium at, for example, a temperature of about 10 °C. to about 25°C.

The reaction between the product thus obtained and ammonia can be carried out in the presence of a suitable inert solvent, for example, chloroform by blowing ammonia gas into the reaction mixture. The reaction can be carried out at a temperature, for example, of about 0.degree. C. to about 20.degree. C. The amount and rate at which the ammonia gas is blown in can be suitably chosen. For example, an amount sufficient to form H_2 NH_2 C by the de-HX reaction between X and ammonia at the 3-position XH_2C of the formula (III) compound will do. The resulting formula (II) compound can be directly reacted with acetylsalicylic acid or a reactive acid derivative thereof, but it is preferably used after its purification. The purification can be performed by optional means, for example, by chromatography.

In accordance with another mode, the formula (II) compound can also be obtained by reacting the formula (III) compound directly with ammonia. This amination reaction can be carried out by using, for example, an alcohol saturated with ammonia gas. Alcohols that can be used in this mode include such alcohols as ethanol and methanol. The reaction can be carried out, for example, by saturating ethanol with ammonia gas, adding IABr(III) and stirring the mixture at room temperature for 2 hours.

The formula (I) aspirin-isopropylantipyrine of this invention can be obtained by reacting the formula (II) compound thus obtained with acetylsalicylic acid or a reactive acid derivative thereof. As the reactive acid derivatives of acetylsalicylic acid, there can be mentioned, for example, the acid halides such as chloride and bromide; acid anhydride; and the esters such as the lower alcohol esters (e.g. p-nitrophenylester, N-phthalimide ester).

The reaction can be carried out in a suitable inert solvent, for example in chloroform. The reaction is preferably performed in the presence of a carbodiimide such as

dicyclohexylcarbodiimide in accordance with the method which per se is known in the synthesis of peptides. The reaction mole ratio can be suitably chosen. For example, the acetylsalicylic acid or reactive acid derivative thereof can be used in an amount of about 1.0 moles to about 1.2 moles per mole of the formula (II) compound. The resulting formula (I) aspirin-isopropylantipyrine can be purified, for example, by chromatography.

The novel compound of formula (I) obtained as above described possesses superior analgetic, antipyretic and anti-inflammatory activity, and moreover the gastric ulcerogenic activity and hygroscopicity that are possessed by aspirin are greatly reduced. In addition, there is a reduction in the side effects that result when the pyrazolone derivatives possessing antipyretic and analgetic activity are used. It is thus seen that the formula (I) aspirin-isopropylantipyrine is extremely useful as an analgetic, antipyretic and anti-inflammatory agent.

It is thus possible to provide in accordance with this invention a pharmaceutical composition composed of pharmaceutically effective amounts of aspirin-isopropylantipyrine of formula (I) and a pharmaceutically acceptable carrier or diluent.

As the carrier or diluent, the various liquid or solid carriers or diluents can be used. As examples, there can be named such solid carriers or diluents as lactose, starch, CMC-Na, magnesium stearate and glucose; and such liquid carriers or diluents as propylene glycol, mucilage of acacia, CMC-Na solution, and ethanol.

Various other adjuvants that are usually used in compounding medicines can also be added

The pharmaceutical composition of this invention can be prepared in such various forms for oral administration, as powders, granules, pills, tablets, sugar-coated pills, capsules, solutions and suspensions, and such forms for extrabuccal administration as injections and suppositories.

The amount used of the active ingredient of formula (I) in the pharmaceutical composition of this invention can be suitably chosen. For example, the amount used can be about 10% to about 100%, preferably about 99%, by weight based on the weight of the composition. The active ingredient of formula (I) can also be administered not in the form of a composition, but alone.

The pharmaceutical composition of this invention may contain various other drugs such as antipyreticanalgesic drugs (aminopyrine, antipyrine) and ammonium bicarbonate. The compound of formula (I) of this invention has the advantage that no trouble results in using it conjointly with other drugs, since the formula (I) compound is in itself free of hygroscopicity and is stable.

There is also provided in accordance with this invention a method of treating patients needing an analgetic, antipyretic or anti-inflammatory treatment, the method being characterized by the administration of aspirin-isopropylantipyrine of formula (I).

According to this method, the pharmaceutical composition in a form such as hereinbefore described or the formula (I) compound itself can be administered in a dose of about 0.02 to about 0.08 g/kg-body/day. The composition of the invention can be administered through various routes. Thus, it may be in an orally administrable form, an injectable form, or a parenterally administrable form (e.g., suppository).

Tests of the analgetic, antipyretic and anti-inflammatory adtivities as well as acute toxicity of the aspirin-isopropylantipyrine (AIA), the formula (I) compound of this invention, that were conducted using aspirin as comparison will now be described, along with the results obtained.

(1) Analgetic Activity

The number of writhings that occurred when mice were administered an acetic acid solution intraperitoneally were counted, and the rate of inhibition based on the control group was calculated. The test compounds were administered to the mice 30 minutes before the acetic acid solution was administered. The results obtained are shown in Table 1, below. It is seen that the compound of this invention demonstrates an analgetic activity comparable to that of aspirin.

Further, the prolongation time of pain threshold of mouse tail was determined in accordance with the D'Amour-Smith Method (J. Pharmacol. Exp. Ther., 72, 74 (1941)). After the subcutaneous administration of the test compounds to mice, the tails of mice were exposed to heat and the prolongation time of pain threshold was determined. The results obtained are shown in FIG. 1. Curve A in the figure shows the results obtained in the case of the control group; B_1, the group administered 100 mg/kg of AIA; B_2, the group administered 200 mg/kg of AIA; and C, the group administered 200 mg/kg of aspirin. The group administered 200 mg/kg of AIA was seen to exhibit a stronger analgetic activity than the group administered 200 mg/kg of aspirin.

TABLE1

	Analgetic Activity		
Compound	dose (mg/kg)	No. of Writhings	Inhibition (%)
Control	0	32.2 ± 3.7	—
AIA	50	22.1 ± 3.3	31.4
	100	18.3 ± 1.7	43.2
Aspirin	50	17.2 ± 4.0	46.6
	100	15.3 ± 2.4	52.5

(2) Gastric Ulcerogenic Activity

Immediately after ligation of the pylorus of fasted rats, the test compounds were administered orally. The stomachs were removed 7 hours later, and the lengths of the lesions in the glandular portion were measured. The results obtained are shown in Table 2A, below.

TABLE 2A

	Gastric Ulcerogenic Activity (Pylorus-ligated rats)	
Compound	Dose (mg/kg)	Length of Stomach Lesion (cm)
AIA	100	0.11 ± 0.09
Aspirin	100	4.13 ± 1.24

On the other hand, after administering an adjuvant, the rats were orally administered 200 m/kg of the test compounds per day for 21 days. On the 21st day the stomachs were removed, and

the lengths of the lesions in the glandular portion were measured. The results obtained are shown in Table 2B, below.

TABLE 2B

Compound	Gastric Ulcerogenic Activity (Adjuvant-administered rats) Dose (mg/kg)	Length of Stomach Lesion (cm)
Control	0	0.05 ± 0.048
AIA	200	0.04 ± 0.031
Aspirin	200	3.29 ± 1.37*

*P < 0.05

As is apparent from the results shown in the foregoing Tables 2A and 2B, little or no injury is caused to the stomach by the compound of this invention. It can thus be seen that the gastric ulcerogenic activity possessed by aspirin has clearly disappeared.

(3) Anti-inflammatory Activity

Rats were subcutaneously administered the test compounds, and 30 minutes later a carrageenin solution was administered subcutaneously to the foot pad of the rats. The volume of the hind paw was measured at prescribed intervals after the administration of the carrageenin, and the rate of increase in the volume of the paw was calculated and designated as the rate of swelling (%). The results obtained are shown in FIG. 2. In the figure, curve A shows the results obtained in the case of the control group; B_1, the group administered 100 mg/kg of AIA; B_2, the group administered 50 m/kg of AIA; C_1, the group administered 100 mg/kg (0.56 millimole) of aspirin; and C.sub.2, the group administered 50 mg/kg of aspirin.

On the other hand, an adjuvant was administered subcutaneously to only the foot pad of the left hind paw, and 200 mg/kg per day of the test compounds were administered daily for 21 days. The rate of increase in the volume of the both hind paws were measured daily and designated as the rate of swelling (%). The results obtained are shown in FIG. 3. Curve D_1 in the figure shows the results obtained in the case of the left hind paws of the control group (adjuvant administered); D_2, the right hind paws of the control group (adjuvant not administered); E_1, the left hind paws of the AIA-administered group; E_2, the right hind paws of the AIA-administered group; F_2 the right hind paws of the group administered aspirin.

It is seen from these results that the compound of this invention has the activity of inhibiting carrageenin edema formation and that it has an inhibitory effect on adjuvant arthritis comparable to that of aspirin.

(4) Antipyretic Activity

Rats received a sterilized E. coli suspension (1 platinum loop/2 ml saline, 0.5 ml/100 g, i.v.) as a pyrogen, and 2 hours later the test compounds were injected subcutaneously. The temperature was taken at hourly intervals before and after injection of the test compounds.

The compound of this invention demonstrated antipyretic activity in the above test by the subcutaneous administration of 100 mg/kg of the compound.

(5) Additional Activity

The compound of this invention was seen to inhibit the contraction induced in the excised intestinal tract of rats by histamine, acetylcholine and barium chloride, with a concentration of 100 .mu.g/ml.

(6) Acute Toxicity

The acute toxicity of AIA was tested using male mice (ddy, body weight 18-25 g), and the dose at which 50% of the animal population were killed (LD 50) was determined. The results obtained are shown in Table 3. It is seen that the toxicity of AIA is extremely low as compared with that of aspirin.

TABLE 3

Compound	Acute Toxicity LD 50 (g/kg) Oral administration	Subcutaneous administration	Intraperitoneal administration
AIA	>5.0	>5.0	3.67 ± 0.07
Aspirin	11.6 ± 0.07	1.02 ± 0.11	0.76 ± 0.09

Experimental
Production of Compound

(a) Chloroform (180 ml) was added to 30.9 g (0.1 mole) of 2-methyl-3-bromomethyl-1-phenyl-4-isopropylpyrazolone (III) and 14.7 g (0.105 mole) of hexamethylenetetramine, and the mixture was refluxed for 2.5 hours. The chloroform was then distilled off under reduced pressure, after which 600 ml of an ethanol/hydrochloric acid (1:1) mixture was added, and the reaction mixture was stirred at room temperature of 36 hours. After completion of the hydrolysis, the solvent was distilled off under reduced pressure. This was followed by the addition of 500 ml of chloroform and blowing of ammonia gas into the mixture. The resulting precipitate of ammonium chloride was filtered off. After the filtrate was concentrated under reduced pressure, chloroform was added and the operation of concentrating under reduced pressure was repeated five times to eliminate the remaining ammonia.

After dissolving the resulting concentrate in 100 ml of chloroform, the solution was added to a column packed with B 1.4 liters of silica gel (WAKOGEL C-200) and eluted stagewise, using chloroform and methanol. Specifically, chloroform, chloroform/methanol (100:1), chloroform/methanol (50:1) and chloroform/methanol (20:1) were successively eluted. The eluates were then analyzed by thin-layer chromatography [WAKOGEL B-5, developing solvent: chloroform/methanol (9:1), color reagent: iodine vapor, ninhydrin]. The eluted fractions exhibiting only the spot at R_f =0.35 were collected and concentrated under reduced pressure to give 19.6 g of 2-methyl-3-aminomethyl-1-phenyl-4-isopropylpyrazolone (II) (yield 80%) as an oily product.

(b) 2-Methyl-3-bromomethyl-1-phenyl-4-isopropylpyrazolone (II) (30.9 g) was

dissolved in 2000 ml of ethanol saturated with ammonia gas, and the solution was stirred at room temperature for 2 hours. After distilling the solvent off under reduced pressure, the reaction mixture was separated and purified by chromatographing on a column of silica gel by operating as in (a), above, to give 9.8 g (yield 40%) of 2-methyl-3-aminomethyl-1-phenyl-4-isopropylpyrazolone (II).

(c) Aspirin (14.4 g, 0.08 mole) was dissolved in 400 ml of chloroform, after which the solution was cooled to 0.degree. C. Dicyclohexylcarbodiimide (18.2 g, 0.088 mole) was then added to the solution followed by stirring the mixture for 30 minutes and thereafter adding 19.6 g (0.08 mole) of 2-methyl-3-aminomethyl-1-phenyl-4-isopropylpyrazolone (II) obtained in either (a) or (b), above. The mixture was then stirred at room temperature for 24 hours. The precipitate of dicyclohexylurea formed was filtered off, and the solvent was distilled off under reduced pressure.

The residue was dissolved in 150 ml of chloroform, and this solution was added to a column packed with 1.8 liters of silica gel (WAKOGEL G-200), and its stagewise elution was performed as in (a), above, using chloroform and methanol. The eluates were analyzed by thin-layer chromatography [under the same conditions as in (a), except that iodine vapor and sulfuric acid were used as color reagent]. The eluted fractions exhibiting only the spot at R_f =0.52 were collected and concentrated under reduced pressure. The concentrate was purified by crystallizing from ethyl acetate to give 25.4 g (yield 80%) of N-3'a-propylphenazonyl-2-acetoxybenzamide (I).

This product is white crystals melting at 140.degree.-141.degree. C. This product dissolves readily in methanol, ethanol and acetone and dissolves fairly well in chloroform but is practically insoluble in water. In thin-layer chromatography (WAKOGEL B-5, color reagent: iodine vapor, sulfuric acid) this compound exhibits an R_f =0.52 when chloroform/methanol (9:1) is used as the developing solvent and an R_f =0.23 when ether is used as the developing solvent.

Elementary analysis:

	C	H	N
Calcd. (%) for $C_{23}H_{25}N_3O_4$:	67.81	6.14	10.32
Found (%):	67.82	6.07	10.29

Pharmaceutical Compositions

Tablets:

The following ingredients are contained in the amounts indicated in each tablet (500 mg).

AIA	250.0 mg
Cornstarch (exipient)*	120.0 mg
Lactose (excipient)*	122.5 mg
Hydroxypropyl cellulose (binder)*	5.0 mg
Talc (lubricant)*	1.5 mg
Magnesium stearate (lubricant)*	1.0 mg
Total	500.0 mg

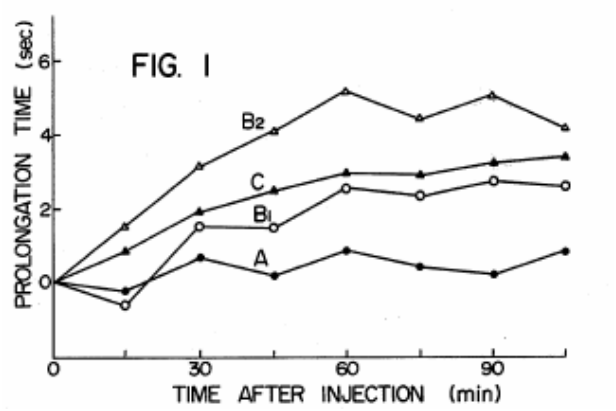
*Japanese Pharmacopeia

Granules:

The following ingredients are contained in the amounts indicated in each gram of the granules.

AIA	500.0 mg
Lactose (exipient)	250.0 mg
Cornstarch (exipient)	200.0 mg
Crystalline cellulose (disintegrator)	30.0 mg
Hydroxypropyl cellulose (binder)	20.0 mg
Total	1000.0 mg

Aspirin (acetylsalicylic acid) is being widely used as a relatively safe antipyretic, analgetic and anti-inflammatory agent. It however has the drawback that it has a gastric ulcerogenic activity, with the consequence that it causes nausea and loss of appetite and even induces such gastric disorders as peptic ulcer, hemorrhage of stomach, etc. at times. Especially, in the case where aspirin is administered in large doses say for treatment of rheumatic diseases, care must be exercised to guard against gastric disorders ascribable to the ingestion of aspirin. Furthermore, aspirin is hygroscopic, and hence aspirin not only is decomposed by moisture but when it is mixed with other drugs, for example, other antipyretic and analgetic preparations, it becomes moist and discolored at times.



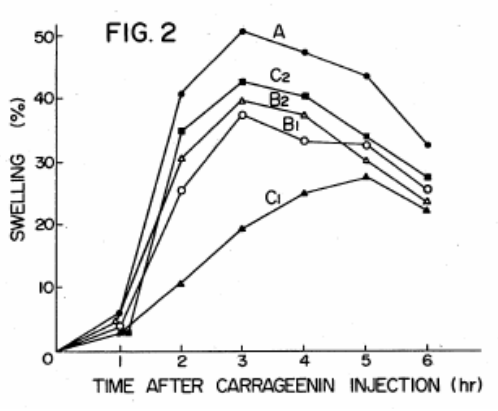
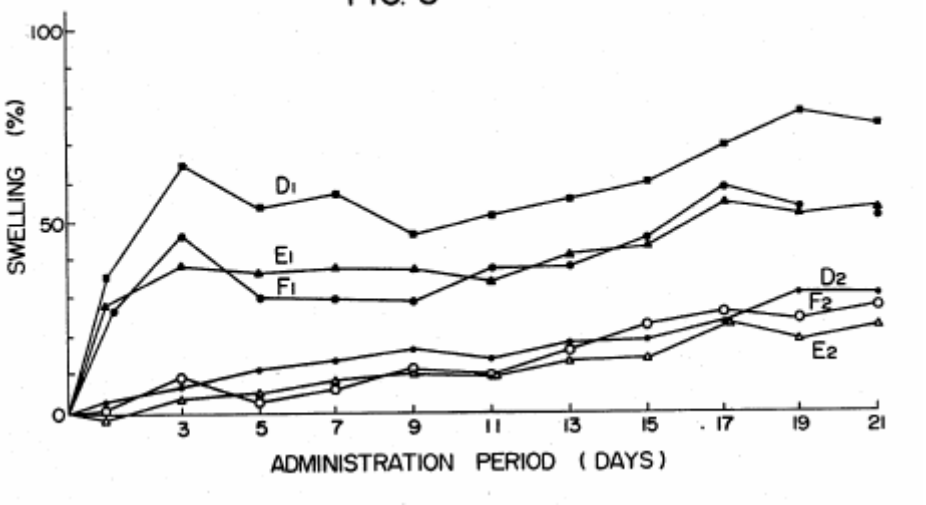


FIG. 3


100
50
0
SWELLING (%)
D1
E1
F1
D2
F2
E2
3
5
7
9
11
13
15
17
19
21
ADMINISTRATION PERIOD (DAYS)

****

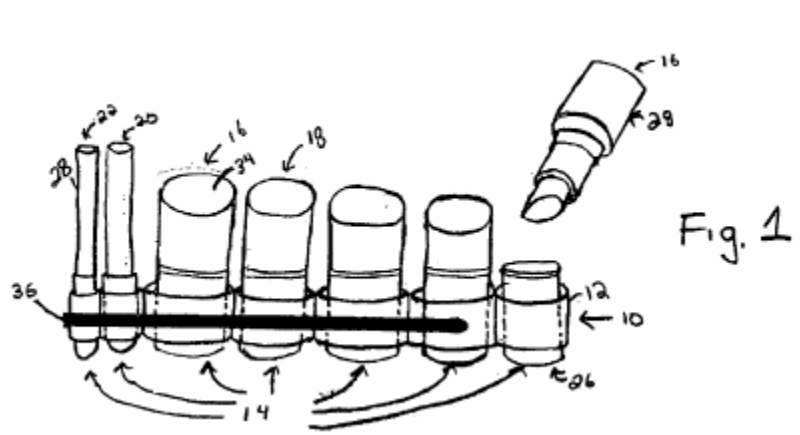


Fig. 1

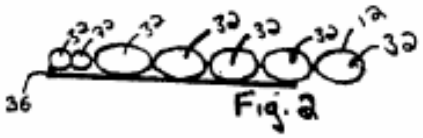


Fig. 2

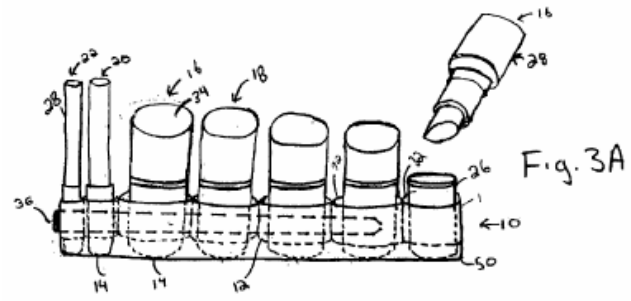


Fig. 3A

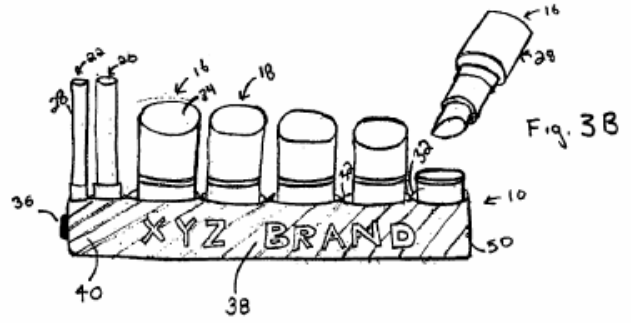


Fig. 3B

Figures

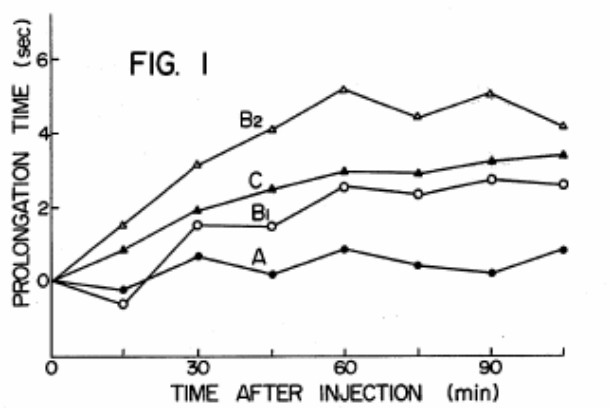


FIG. 1
PROLONGATION TIME (sec)
0
2
4
6
B2
C
B1
A
0
30
60
90
TIME AFTER INJECTION (min)

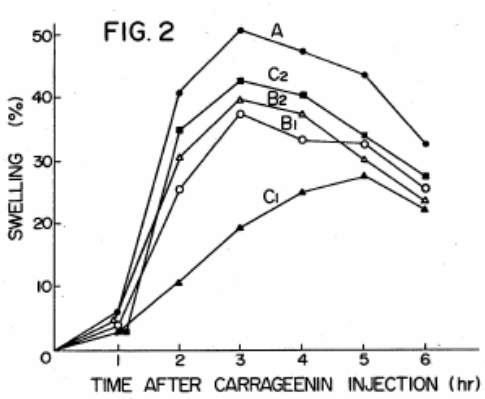


FIG. 2
SWELLING (%)
0
10
20
30
40
50
A
C2
B2
B1
C1
1
2
3
4
5
6
TIME AFTER CARRAGEENIN INJECTION (hr)

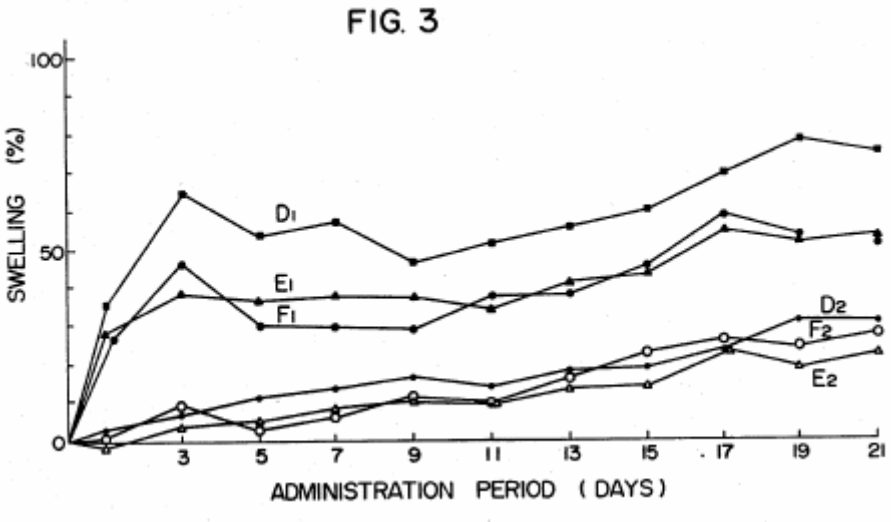


FIG. 3
SWELLING (%)
0
50
100
D1
E1
F1
D2
F2
E2
3
5
7
9
11
13
15
17
19
21
ADMINISTRATION PERIOD (DAYS)

Figures