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J. Wojcicki et al Zbl, Pharm, 118 (1979) Vol. 2—3
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(54) Analgesic compositions

(57) A therapeutic dose comprising 60—1200 mg of a conventional antiacid component and 150—2000 mg of N-acetyl-p-aminophenol makes possible an increased rate of absorption of the latter into the blood stream of a subject. The compositions may be administered orally and may also comprise aspirin, phenylpropanolamine hydrochloride, chlorpheniramine maleate, and dextromethorphan hydrobromide.

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SPECIFICATION

Analgesic compositions

This invention relates to analgesic compositions containing N-acetyl-p-aminophenol (hereinafter referred to as APAP) and to processes involving the administration of such compositions to subjects and especially human subjects. More particularly, it concerns compositions of this above character that have relatively high absorption rates as measured by the time it takes after ingestion for the level of APAP to reach its maximum in the blood plasma of the subject (t max.).

APAP has long been known in the pharmaceutical and medical arts to be useful as an analgesic and/or antipyretic agent and has found its way into several commercially available products including tablets, capsules, and liquids. Subsequent to ingestion of APAP, the rate of onset of the intended pharmacologic action is often slower than desired and also quite variable from subject-to-subject. Such slowness and variability apparently result from the fact that absorption of APAP from the gastrointestinal tract into the bloodstream is inhibited as a consequence of the process usually used in making these products.

It has now been found that the rate of absorption of APAP into the bloodstream as measured by the t max, can be increased if the APAP is coadministered with a dose of an antacid that falls in the range of from about 60 mg to about 1200 mg with the preferred range being from about 400 mg to about 1000 mg and the optimum range being from about 450 mg to 880 mg. The weight of antacid used will depend on its milliequivalent weight.

It is accordingly an object of the present invention to provide an analgesic composition containing APAP that has a relatively high absorption rate.

It is also an object of the present invention to provide processes which entail administering the compositions of the aforesaid object to subjects and particularly human subjects.

Other and more detailed objects of this invention will be apparent from the following description and claims.

The increase in APAP absorption rate with the compositions of this invention has been most readily demonstrated on so-called slow APAP absorbers. For the purposes of this invention, those subjects who had less than 2 μg/ml of plasma APAP at 10 minutes after they were given APAP alone at the recommended dose i.e. 650 mg. without an antacid were considered as slow absorbers.

It has been suggested in the prior art to simultaneously administer as a single oral dose 4.0 g (i.e. 4000 mg) of calcium carbonate with paracetamol tablets (i.e. 1 gm of APAP) (J. Wojcicki et al, Zbl, Pharm, 118 (1979) Vol. 2—3). These were administered by Wojcicki et al to investigate the pharmacokinetics of paracetamol. It was found in this study that when 4 grams of $CaCO_3$ were administered with 1 gm of APAP that in fact there was a significant decrease in the rate of absorption as measured by the t max. As shown in Table 5, (p. 289 of the Wojcicki et al article) the t max for APAP alone was 1.4 hours; whereas, the t max for $CaCO_3$ and APAP was 1.9 hours. In other words, the time it took for the plasma level of APAP to reach its maximum was 1/2 hour longer when the APAP was coadministered with 4 gm (4000 mg) of $CaCO_3$ as compared with the case when the APAP was administered without the $CaCO_3$.

As will be shown in more detail below, when the antacids are administered at the levels prescribed in the present invention along with the APAP, the results are reversed. The t max values are lower in the case where the antacid at the levels prescribed in the present invention is administered along with the APAP as compared with the case where the antacid is eliminated.

The APAP and antacid may be administered in a variety of fashions according to the present invention. They may, for example, be administered as two separate tablets; that is, as an APAP tablet and a separate antacid tablet which can be taken simultaneously or serially. They may also be administered in the form of a novel single layer or two layered tablet. In the latter case, the antacid will ordinarily be contained in one layer and the APAP will be contained in the other layer.

They may also be administered in the form of novel capsules in which the powdered or granular APAP is intimately mixed with the powdered or granular antacid. In a modification of the capsule product, one of the components may be present in the capsule as one or more small tablets and the other as a powder or granular preparation.

The APAP and antacid can also be taken in liquid form as solution or suspension of one or more of the active ingredients. In this case, suitable stabilizers, emulsifiers, and/or suspending agents may be used to maintain the antacid or APAP in suspension or solution.

Any antacid or combinations thereof commonly used to neutralize stomach acids may be used in the compositions or processes of the present invention. Such antacids are listed in the Handbook of Non-Prescription Drugs, 6th Edition, 1979, p. 1—19 or the OTC Antacid Monograph. By way of example, mention may be made of calcium carbonate, magnesium carbonate, sodium bicarbonate, sodium carbonate, potassium bicarbonate, aluminum hydroxide, aluminum oxide, magnesium oxide, magnesium hydroxide, magnesium trisilicate, aluminum glycinate, dihydroxyaluminum acetate and mixtures thereof. Of special interest are calcium carbonate, magnesium carbonate, a combination of calcium carbonate and magnesium carbonate, sodium bicarbonate and magnesium hydroxide. When calcium carbonate and magnesium carbonate are employed together, they may be used in the weight

ratio of from about 5:1 to 1:5 and preferably in the ratio of 2:1.

As indicated previously, the level of antacid that will be coadministered with the APAP or contained in the dosage forms of this invention may vary from 60 mg to about 1200 mg. However, the preferred range is from about 400 mg to 1000 mg with the optimum range being from about 450 mg to 880 mg.

The quantity of APAP which will be administered with the antacid or contained in the dosage forms of this invention may also vary. Usually, it will fall in the range of from about 150 mg to 2000 mg with the preferred range being from about 250 mg to 1000 mg.

In addition to the antacid and APAP contained in the compositions of this invention, they may also include other pharmaceutically active ingredients. These may be other analgesics, antihistamines, decongestants, cough suppressants, etc. By way of more specific illustration of the other pharmaceutically active ingredients that may be employed, mention may be made of aspirin, phenylpropanolamine hydrochloride, chlorpheniramine maleate, dextromethorphan hydrobromide, etc.

When the compositions of the present invention take the form of tablets, they may also contain adjuvants conventionally included in compositions of this general character. Thus, for example, they may contain a binder which is exemplified by such materials as: lactose, dextrose, starch, polyvinylpyrrolidone (PVP), sucrose, gelatin; natural gums such as acacia, tragacanth, pectin, guar, karaya; cellulose derivatives such as methyl cellulose USP, sodium carboxymethyl cellulose USP, hydroxypropylmethyl cellulose USP (Methocel HG), hydroxypropyl cellulose (Klucel), ethyl cellulose NF, or avicel microcrystalline cellulose NF. The quantity of binder included in these compositions may vary somewhat. Generally, it will be no greater than the amount of APAP in the tablet and preferably no greater than one half of the amount of APAP contained in the tablet. Usually, each tablet will contain from about 10 to about 300 mg of binder.

Another tablet adjuvant that may be added to the tablets of the present invention is a disintegrant. Typical disintegrants include starches; modified starches such as sodium carboxymethyl starch, microcrystalline cellulose; water soluble cellulose derivatives such as methyl cellulose or sodium carboxymethyl cellulose or clays. The quantity of disintegrant in the present tablet may also vary but usually will be in the range of from 10 to 500 mg per tablet.

When the composition of this invention take the dosage form of a capsule, it may also contain additives that are conventionally included in this type of dosage forms. Thus, it may include such things as flow aids (e.g. silicone fluid, Cab-O-Sil, talc, metallic stearates, stearic acid), wetting agents (e.g. SLS). Usually, the total quantity of capsule adjuvants may vary and may be related to the amount of APAP contained in the capsule. Typically, this will amount to from about 0.1% to 15% by weight based on the weight of the APAP in the capsule.

The compositions of the present invention may be administered in unit dosage forms that contain varying amounts of the active ingredients (i.e. APAP and antacid). Furthermore, to administer the required dose of active ingredients, it is possible to give the subject one or more of the unit dosage forms. It is to be understood that when the term dose is used herein and in the appended claims, it is intended to cover the quantity of active ingredients administered at a single administration of the composition irrespective of whether one or more unit dosage forms are given as tablets, capsules, teaspoonfuls, etc. It is also intended to cover the situation in which some or all of one active ingredient (i.e. APAP or antacid) is contained in one unit dosage form and some or all of the active ingredient is contained in another unit dosage form.

The following Examples are given to further illustrate the present invention. It is to be understood, however, that of the invention is not limited thereto.

EXAMPLE 1

Two-Layered Tablet

Ingredients	mg/tab
LAYER I: APAP Layer	
Acetaminophen, powder	325.000
Cellulose, microcrystalline	147.500
Sodium carboxymethyl starch	55.000
Colloidal silicon dioxide M—5	2.500
Deionized water	12.500
Stearic acid, powdered	2.500
Methylparaben	0.545
Propylparaben	0.218
	545.763

Dry blend the above ingredients.

LAYER II: Alkaline Layer	
Calcium carbonate	200.000
Magnesium carbonate	100.000
Corn starch as aqueous starch paste (10%)	20.000
Corn starch	40.000
	360.000
Moisture: 2.0% Grand total	905.763

Blend $CaCO_3$, $MgCO_3$ and corn starch, and granulate with 10% starch paste in a pony mixer pot. Screen wet granulation through 4 mesh screen and dry in a Glatt, and screen through 8 mesh and 12 mesh screen.

The mixture described above under "Layer I" is charged into a tablet punch and preferably tamped down lightly. The mixture described under "Layer II" is then fed into the tablet punch and top of "Layer I" and the combination is compressed to form a two layered tablet.

EXAMPLE 2

Homogeneous Tablet: Formula #1428

Item No.	Ingredients	mg/tab
Part I		
1	Acetaminophen, powd.	500.00
2	Starch, corn	44.25
3	Stearic acid, powder	4.75
4	Methylparaben	0.55
5	Propylparaben	0.20
6	Povidone K—29—32 (polyvinyl-pyrrolidone)	0.25
7	Water, deionized	
		550.00
Part II		
8	Sodium bicarbonate, #5 gran.	225.00
		775.00

Procedure:

Part I

A. In a mixer, place half of 1, and all of 2, 3, 4 and 5, and mix.

B. Dissolve 6 in 7 which has been heated to 100°C.

C. Immediately add 3/4 of B to mixture A, mix well, add the remaining half of 1, and mix well again.

D. Add remaining 1/4 of B, mix for 5 minutes.

E. Pass damp granulation D through Oscillator, 6 mesh screen.

F. Dry in Fluid Bed Dryer, inlet temp. 55°C, until outlet temp. reaches 40—44°C (moisture content 3%, see below).

G. Pass through Oscillator, 20 mesh screen, (.027" opening).

Part II

A. Dry 8 in Fluid Bed Dryer for 2 minutes at 35°C (if caked).

B. Blend Part I with 8 for 5 minutes.

C. Compress to the specifications below.

Appearance: White tablet
Moisture: Part I gran. 3% (180°F oven, 30 min.)
Punch: 15/32" SCU
Weight: 775 mg.
Thickness: .255" ± .005"
Hardness: 10—14 SCU
Disintegration: 30 Sec., USP Basket App. 37°C

EXAMPLE 3

Homogeneous Tablet — Sodium Bicarbonate Formula — Formula #1455

Item No.	Ingredients	mg/tab
Part I		
1	Acetaminophen, spec. podw.	325.0000
2	Starch, corn	28.7625
3	Methylparaben	0.3575
4	Propylparaben	0.1300
5	Povidone (K—29—32) (PVP)	0.1625
6	Stearic acid, powd.	3.0875
7	Water, deionized	
		357.5000
Part II		
8	Sodium bicarbonate#5 granular	225.0000
		582.5000

Procedure:

Part I

Same as for Part I in Example 2 above, but pass through 12 mesh screen Oscillator.

Part II

A. If caked, 8 may be dried for 2 minutes at 35°C in Fluid Bed Dryer.
B. Blend 8 and Part I for 5 minutes.
C. Compress to specifications below.

Appearance: White tablet
Moisture: Part I gran. 3—4% (180°F oven, 30 min)
Punch: 7/16" SC
Weight: 582.5 mg ± 5%
Thickness: 0.210" ± .005"
Hardness: 7—9 SCU (Heberlein)
Disintegration: USP Basket 37°C water, 30 sec. 25°C water <1 min.

To compare the absorption rate for APAP, as measured by the t max when APAP is administered with and without the coadministration of antacids, the following tests were carried out:

A contemporaneous cross-over study comparing the free n-acetyl para-aminophenol (FAPAP) plasma concentrations produced in a panel consisting of between 15 and 50 healthy volunteers was conducted.

The study usually begins between 7:00 and 8:00 a.m. Subjects are instructed to fast after their evening meal the night before. After the subjects assemble in the morning, the test product is administered along with 100 ml of water. Blood samples are taken precisely 10, 20, 40 and 60 minutes post administration.

Plasma is separated from the blood samples, and the FAPAP concentration is determined using a high pressure liquid chromatography procedure. Administration of different products in the cross-over study is at least one week apart.

Four studies were run identified as studies BC 5—75, BC 9—76, BC 24—77 and BC 1—81 respectively. In study BC 5—75 two tablets of a commercial APAP tablet (Tablet D) each containing 325 mg of APAP were administered to the test subjects and t max was measured. This was compared with the results obtained when 2 Tablets D each containing 325 mg of APAP were coadministered with 2 chewable $CaCO_3$ tablets each containing 440 mg of $CaCO_3$. The composition of each of these tablets is given below:

TABLET D

Ingredients	mg/tab
Acetaminophen, powder	325.0
Cellulose, microcrystalline	75.0
Starch, corn	75.0
Sodium lauryl sulfate, phosphate buffered	1.0
Povidone (K—29—32)	5.0
Water, deionized	
Polyethylene glycol 6000 (fine powd.)	1.25
	482.25

$CaCO_3$ TABLET

Ingredients	mg/tab
Calcium carbonate	440.0
Corn starch as aqueous paste (10%)	20.0
Dextrose monohydrate	540.0
Stearic acid, powder	10.0
	1010.0 mg

In study BC 9—76 two Tablets D (each containing 325 mg of APAP) were administered to the test subjects and the t max was measured. This was compared with the results obtained when two tablets of Example 1 above (i.e. the two layered tablet) each containing 325 mg of APAP, 200 mg calcium carbonate and 100 mg magnesium carbonate were administered to the subjects.

In study BC 24—77 two tablets of an extra strength commercial APAP tablet (Tablet T) each containing 500 mg of APAP were administered to the test subjects and the t max was measured. The formula for Tablet T is given below:

TABLET T

Ingredients	mg/tab
APAP	500.0
Inert ingredients	165.0

This was compared with the results obtained when two tablets of Example 2 Formula 1428 (i.e. the single layer homogeneous tablet) each containing 500 mg of APAP and 225 mg of sodium bicarbonate was administered to the subjects.

In Study BC 1—81, two tablets of a commercial 325 mg APAP tablet (Tablet t) were administered to test subjects and the t max was measured. The formula for tablet t is given below:

TABLET t

Ingredients	mg/tab
APAP	325.0
Inert ingredients	228.0

This was compared with the results obtained when two tablets of Tablet t were administered along with a chewable tablet containing 400 mg of $CaCO_3$ (Tablet C). The formula for Tablet C is given below:

TABLET C

Ingredients	mg/tab
Calcium carbonate (Sturcal "H")	440.0
Corn starch (as 10% starch paste)	20.0
Dextrose monohydrate	540.0
Stearic acid, powder	20.0
Cellulose microcrystalline (Avicel PH 105)	20.0
	1040.0

Two tablets of Example 1 were also given in this study, as well as two tablets containing 325 mg. of APAP and 225 mg. of $NaHCO_3$ (Tablet B — Formula 1455). The formula for Tablet B is given in Example 3 above.

The results of these tests are summarized in the Table below:

TABLE I

Study	Product	Av. of the Individual Peak Time in Min. (t max)
BC 5—75	Tablet D (325 mg APAP) 2 tab.	43
	Tablet D (325 mg APAP) 2 tab. + $CaCO_3$ 2 tab.	32
BC 9—76	Tablet D (325 mg APAP) 2 tab.	36
	Tablet of Example 1 (325 mg APAP, 200 mg calcium carbonate & 100 mg magnesium carbonate) 2 tab.	30
BC 24—77	Tablet T (500 mg APAP) 2 tab.	42
	Tablet of Example 2 (500 mg APAP and 200 mg $NaHCO_3$) 2 tab.	29
BC 1—81	Tablet t (325 mg APAP) 2 tab.	38
	Tablet t (325 mg APAP) 2 tab. + Tablet C (440 mg $CaCO_3$)	36
	Tablet D (325 mg APAP + 225 mg $NaHCO_3$) 2 tab.	30
	Tablet of Example 1	33

As will be clear from the above Table, each study demonstrated a significant increase in absorption rate as measured by the t max value, that accompanied the administration of the compositions of this invention. These increases are in the range of from about 7% to about 31%.

CLAIMS

1. A therapeutic dose comprising from about 60 mg to about 1200 mg of an antacid component and from about 150 mg to about 2000 mg of N-acetyl-p-aminophenol.

2. A therapeutic dose according to Claim 1 in which said antacid component is present in the range of from about 400 mg to about 1000 mg.

3. A therapeutic dose according to Claim 1 or 2 in which said N-acetyl-p-aminophenol is present in the range of from about 250 mg to about 1000 mg.

4. A therapeutic dose according to Claim 1, 2 or 3 in which said antacid component is present in the range of from about 450 mg to about 880 mg.

5. A therapeutic dose according to Claims 1—4 in which said antacid component is a single antacid.

6. A therapeutic dose according to Claim 5 in which the antacid is calcium carbonate.

7. A therapeutic dose according to Claim 5 in which the antacid is sodium bicarbonate.

8. A therapeutic dose according to Claims 1—4 in which said antacid component is a combination of antacids.

9. A therapeutic dose according to Claim 8 in which said antacid component is a combination of $CaCO_3$ and $MgCO_3$.

10. A therapeutic dose according to Claim 9 in which the weight ratio of $CaCO_3$ to $MgCO_3$ is in the range of from about 5:1 to about 1:5.

11. A therapeutic dose according to Claim 10 in which the weight ratio of $CaCO_3$ to $MgCO_3$ is 2:1.

12. A therapeutic dose according to Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11 in the form of one or more tablets.

13. A therapeutic dose according to Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11 in the form of one or more two-layered tablets, essentially all of the antacid component being contained in one layer and essentially all of the N-acetyl-p-aminophenol being contained in the other layer.

14. A therapeutic dose according to Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11 in the form of one or more capsules containing said antacid component and said N-acetyl-p-aminophenol.

15. A therapeutic dose according to Claim 14 in which either the antacid component or the N-acetyl-p-aminophenol is present as a tablet contained within the capsule and the other component is present as a powder or granulation.

16. A process for increasing the rate of absorption for APAP which comprises administering to a person the therapeutic dose defined in Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

17. A process according to Claim 16 in which the person is a slow APAP absorber.

18. A therapeutic dose according to Claim 1, substantially as described in any of the foregoing Examples.

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