RISK PROFILE

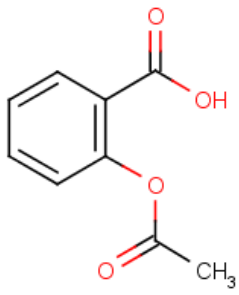
Acetylsalicylic acid

CAS No.50-78-2

Date of reporting 14.02.2012

Content of document

1. Identification of substance

Chemical name (IUPAC):	O-acetylsalicylic acid
INCI	Acetylsalicylic acid
Synonyms	2-Acetoxybenzoic acid, Acidum salicylicum, Aspirin, O-Acetylsalicylic acid, Polypiryna, Salicylic Acid Acetate
CAS No.	50-78-2
EINECS No.	200-064-1
Molecular formula	$C_9H_8O_4$
Chemical structure	
Molecular weight	180.2
Contents (if relevant)	
Physiochemical properties	Appearance: White crystalline powder Density: 1.4 g/cm^3 Boiling point: Decomposes below boiling point at 140°C

	Melting point: 135°C Log P_{ow}: 1.19 Vapor pressure: 0.004 Pa at 25° Solubility in water: poor (0.25 g/100 ml at 15°C) References: (IPCS [online]).

2. Uses and origin

Uses	➢ **Cosmetic products:** *Functions according to:* ○ CosIng database *Delisted 12th May 2010.* Functions not reported (CosIng [online]). *Concentrations being applied* Not reported. *Frequency of use* 5 products were found at a search at EWG`s Skin Deep all being after shave products.. In a search at Codecheck.info, acetylsalicylic acid (ASA) showed up as an ingredient in two cosmetic products; a leave-on aftershave cream for men and women and an aftershave product. The aftershave product description states that the product will prevent razor bumps and ingrown hairs, and should be applied twice a day. On the website for aftershave product, there are two more products containing ASA; a non-spray deodorant and a liquid nail hardener. The function of the acetylsalicylic acid in the non-spray deodorant is stated on the company webpage to be as a *deodorizing agent* - reduces or masks unpleasant body odours. The function of ASA in the other two products are not given. (Codecheck [online]; EWG's Skin Deep [online]). According to a search on the internet ASA is used as the active ingredient (3rd place in the list of ingredients) in a product claiming • Relieves redness & calms sensitive skin—even if you have rosacea • Antioxidants help reduce the signs of aging • Minimizes irritation from shaving & other forms of hair removal • Helps prevent ingrown hairs & razor burn • Reduces redness & inflammation from acne, sunburn, and other skin irritations (For web address see references, online: www.paulaschoice.com.au) There is also a lip balm on sale that contains ASA. – online: http://www.goodguide.com/products/366206-dr-ts-spf-uva In addition, Annex 1 lists topical products that contain salicylic acid and derivatives among which there might possibly also be products falling within the scoop of the cosmetics regulation and that contain

	ASA..[1] ➢ **Medicinal products/applications** ASA (aspirin) is a common nonsteroidal anti-inflammatory drug (NSAID) used in the treatment of pain, fever and inflammation. In addition, it is also used in the prevention of cardiovascular disease, and has been suggested to be an effective chemopreventive agent against cancer. ➢ **Food and drinking water** Data not retrieved.
Origin Natural (exo /endo) Synthetic	Synthetic

3. Regulation

Norway	No regulation
EU	No regulation
Rest of the world	The use of ASA in cosmetic products is prohibited in Canada (Health Canada [online]).

4. Relevant toxicity studies

Absorption Skin	There is limited data on dermal absorption of ASA. One study showed that the bioavailability of topical ASA was in the range of 4-8% of the applied dose (Cryer et al., 1999). 12 - 22 % of the topically applied dose of methyl salicylate (a related substance) was found to be systemically bioavailable (Roberts et al., 1982; Morra et al., 1996). In vitro skin penetration rate (rat skin) of 29% was reported using petrolatum as a vehicle (Edetox database, Annex 2). Other reports suggest that ASA is readily absorbed in human skin (Annex 3). A recent study provides evidence for the feasibility of transdermal low-dose aspirin patch containing lemon oil as penetration enhancer in clinical situations. Thus, the report found excellent release of the drug, and its influence on the blood coagulation by means of affecting both the extrinsic coagulation system and the intrinsic coagulation system (Shamsher et al., 2010). Thus, ASA has the potential to reach the systemic circulation after topical application. However, since data on dermal absorption of ASA is limited, a conservative default value of 100 % absorption will be used.

[1] http://www.pkwy.k12.mo.us/pierre/documents/TopicalProd.pdf

GI tractus	After oral administration, aspirin is rapidly absorbed from the small intestine (Norwegian Medicines Agency [online]).
Distribution	Binding to plasma proteins is concentration dependent, and 66-98 % of salicylic acid is bound (Norwegian Medicines Agency [online]). The volume of distribution is 0.1-0.2 L/kg (Levy et al., 1972).
Metabolism	Following oral administration, ASA (aspirin) is rapidly hydrolysed to salicylic acid, which is used in a wide range of cosmetic products. The plasma salicylate half-life following therapeutic doses is 2 to 4.5 h, but increases to 18 to 36 h in the case of an overdose (Done, 1960). Approximately 80% of salicylic acid is metabolised in the liver. Salicylic acid in conjugation with glycine, forms salicyluric acid and with glucuronic acid forms salicyl acyl and phenolic glucuronide. These metabolic pathways have only a limited capacity. Small amounts of salicylic acid are also hydroxylated to gentisic acid. With large salicylate doses the kinetics switch from first order to zero order (Levy et al., 1972).
Excretion	Salicylates are excreted mainly by the kidney as salicyluric acid (75%), free salicylic acid (10%), salicylic phenol (10%) and acyl (5%) glucuronides, and gentisic acid (< 1%).
Local toxic effects Irritation Sensitivity	There are only limited data regarding skin irritation after topical application of ASA. The topical application of ASA at a dosage of 2 g/kg to rabbit did not cause any skin irritation or sensitivity (SCCNFP, 2001).
Systemic toxic effects	There is no available toxicity data on systemic effects after dermal exposure to ASA. The data below are therefore based on oral exposure.
Acute and repeated dose	In humans, intake of doses of >10 g ASA in adults or > 4 g in children can be fatal (Norwegian Medicines Agency [online]). Oral doses of ASA of 100 mg/kg or higher induce salicylism (a toxic syndrome caused by excessive doses of ASA or any of the salicylates). Common symptoms are tinnitus, nausea and vomiting (Norsk Legemiddelhåndbok [online]).
Mutagenicity /genotoxicity	ASA was negative when tested for in vitro mutagenicity in the Ames test (Kawachi et al., 1980), and in vivo clastogenicity in the Drosophila sex-linked recessive lethal assay (King et al., 1979).
Carcinogenicity	The carcinogenicity of ASA was assessed in rodents. Mice received 1 and 5% and rats received 0.25% and 2% ASA in drinking water. The results were negative for both mice and rats (Odashima, 1980). Epidemiological studies have shown an association between intake of ASA and reduced risk of colorectal cancer (Rothwell et al., 2010).
Reproductive toxicity / teratogenicity	Administration of 200 mg/kg/day of ASA for the last six days of gestation were studied in rats. A prolongation of gestation and parturition time and foetal deaths was observed. The foetal deaths were believed to be attributed to the prolonged parturition time caused by the effects of ASA on prostaglandins synthesis (Tuchmann-Duplessis et al., 1975). This was consistent with the findings of another study, where daily administration of 261 mg/kg/day gave a significant increase in gestation length. In this study, administration of ASA also induced maternal toxicity as reduction of body weight and food consumption (Procter & Gamble, 1994e). Several studies have explored the teratogenic potential of ASA in animals. ASA was administered by oral or parental route at various times during gestation at different doses (ranging form 75 to 500 mg/kg/day) in

Other effects	rats, mice or monkeys. Foetal malformations (such as skeletal malformations and cleft lip), resorption and foetal death (Trasler, 1965;Wilson et al., 1977; Tanaka et al., 1973; Nakatsuka et al., 1979). **Gastric mucosal damage** Low-dose ASA, commonly 75-160 mg, is one of the most widely used drugs for the prevention of serious cardiovascular events, as it reduces the events by 25% in patients at high cardiovascular risk (Antiplatelet Trialists' Collaboration, 1994; Berger et al, 2008). However, studies have shown that even low doses of ASA and non-steroidal anti-inflammatory drugs (NSAIDs) in general, can cause gastric mucosal damage (Fortun et al., 2007; Wolfe et al., 1999; Davies et al, 1997). One study in rats showed that orally and parental administered NSAIDs were equally damaging to the gastric mucosa (Skeljo et al, 1993). In support of this, several human clinical studies and one meta-analysis have shown that enteric-coated formulations of ASA (which are designed to prevent ASA release in the ventricle) did not reduce the gastric mucosal damage (Derry et al, 2000; Sorensen et al., 2000; Kelly et al., 1996; Chowdhury et al., 2001; Garcia et al., 2001; de Abajo et al., 2001; Cryer et al., 1999). This suggest that gastric mucosal damage observed after use of NSAIDs is systemically mediated, and therefore topical application of these ASA might induce gastric damage at the same doses as oral.

5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	The NOAEL value is based on data obtained from clinical trials. The therapeutic plasma concentration of ASA for the analgesic and antipyretic effect is estimated to be in the range of 10 to 30 mg/dL (0.7 to 2.2 mmol/L) (Hill, 1973). A blood plasma concentration of 10 mg/dL ASA equals a total amount of 10 mg/kg bw in the body (see Annex 4 for calculation). Doses in the range of 75-325 mg/day are used for cardiovascular prevention (Campbell et al., 2007; Fox et al., 2006). Daily low doses of ASA have been shown to cause gastric mucosal bleeding (Prichard et al., 1989; Yeomans et al., 2009). Thus, as 75 mg/day has been shown to cause gastric mucosal bleeding in humans, we used this value to calculate NOAEL. LOAEL = 75 mg/day / 60 kg (default value) = 1.25 mg/kg bw/day NOAEL = LOAEL/3 [2] = 1.25 mg/kg bw / 3 = 0.42 mg/kg bw/day
Exposure cosmetic products	**Systemic exposure dose (SED) for ASA in humans:** • ***Leave-on aftershave cream for men and women*** Frequency of application: 2/day Concentration in product: 1% = 0.01 [3] Dermal absorption, default value, SCCS: 100% = 1

[2] When making use of the Lowest Observed (Adverse) Effect Level (LO(A)EL) instead of the NO(A)EL, the SCCS usually takes into consideration an additional factor of 3 in the calculation of the MoS. Scientific Committee on Consumer Safety, The SCCS'S notes of guidance for the testing of cosmetic ingredients and their safety evaluation, the 7th revision, p 54.

[3] Note: the used concentration is for illustrative purposes, as the exact concentration in product is unknown.

	Typical body weight of human: 60 kg Skin surface area [4]: men: 305 cm^2, women: 3,150 cm^2. Amount of product applied, men: 1mg/cm^2 (default value, SCCS) x 305 cm^2 x 2/day: 610 mg/day Amount of ingredient, men: 610 mg/day x 1 x 0.01 = 6.1 mg Calculation of SED, men: 6.1 mg / 60 kg = **0.1 mg/kg bw/day** Amount of product applied, women: 1mg/cm^2 (default value, SCCS) x 3,150 cm^2 x 2/day: 6,300 mg/day Amount of ingredient,women: 6300 mg/day x 1 x 0.01 = 63 mg Calculation of SED, women: 63 mg / 60 kg = **1.1 mg/kg bw/day** • ***Non-spray deodorant*** Calculated relative daily exposure (mg/kg bw/day) : 22.08 [5] Dermal absorption, default value, SCCS: 100% = 1 Concentration in product: 1% = 0.01 [2] Calculation of SED: 22.08 mg/kg bw/day x 1 x 0.01 = **0.22 mg/kg bw/day** • ***Liquid nail hardener*** For this product the dermal exposure of ASA will be close to zero, since there will be minimal contact between the applied product and the skin. **Overall SED, men**: 0.1 + 0.22 = **0.32 mg/kg bw/day** **Overall SED, women**: 1.1 + 0.22 = **1.32 mg/kg bw/day**
Margin of Safety (MoS)	NOAEL: 0.42 mg/kg bw/day ***MoS for ASA in leave-on aftershave cream, men:*** SED: 0.1 mg/kg bw/day MoS: 0.42/ 0.1 = 4 ***MoS for ASA in leave-on aftershave cream, women:*** SED: 1.1 mg/kg bw/day MoS: 0.42/ 1.1 = 0.4 ***MoS for ASA in non-spray deodorant:*** SED: 0.22 mg/kg bw/day MoS: 0.42/ 0.22 = 1.9 ***MoS for overall exposure for ASA from cosmetic products, men:*** Total SED, men: 0.32 mg/kg bw/day MoS: 0.42/ 0.32 = 1.3 ***MoS for overall exposure for ASA from cosmetic products, women:*** Total SED, women: 1.32 mg/kg bw/day MoS: 0.42/ 1.32 = 0.3

[4] See annex for calculation.
[5] Estimated daily exposure levels for different cosmetic product types according to Colipa data [SCCNFP/0321/02; Hall et al. 2007, 2011]. Updated SCCS notes of guidance, 8th revision, SCCS/1501/12

6. Other sources of exposure than cosmetic products

Food stuffs	ASA does not occur in food. However, derivates of this compound does; salicylic acid and the salts and esters of this compound (salicylates) occur in a wide variety of foods, such as vegetables, fruits, nuts, seeds and spice. Some salicylates are also used as food flavouring agents. Swain and co-workers estimated that the average amount in the Western diet was in the range of 10-200 mg per person/day (Swain et al., 1985).
Pharmaceuticals	In many countries, pharmaceuticals containing ASA is available without prescription. The daily maximum recommended dose is 4 g for adults. ASA should be used with caution in children, and the recommended maximum dose varies with body weight; 10-15 kg: 150 mg 3 times a day, 15-25 kg: 250 mg 3 times a day, 25-40 kg: 250-500 mg 3 times a day, children>12 years: 500 mg 3 times a day (Norwegian Medicines Agency [online]). For prevention of serious cardiovascular events, low-dose ASA, typically 75 or 81 mg, is used. Pharmaceuticals containing ASA is not recommended for use under these conditions; i) sensitivity for ASA or other salicylates, ii) ulcerative colitis, iii) increased bleeding risk, iv) during first and second trimester. In addition, during the third trimester of pregnancy, only doses of 100 mg/day or less should be used (Norwegian Medicines Agency [online]).
Other sources	
Adverse side effects - from uses other than cosmetics	Use of acetyl salicylic acid (aspirin) during pregnancy has been associated with increased risk of cryptorchidism (Kristensen et al., 2011). Another study did not find an association between maternal use of ASA and cryptorchidism (Jensen et al., 2010). The use of aspirin in children has been restricted by the medicines regulatory authorities in Europe (MacDonald, 2002). The reason for limiting the use of aspirin in children is because of a possible association between aspirin and Reye syndrome, which is a grave reaction of children to certain viral infections, such as chicken pox (Norwegian Medicines Agency [online]).

7. Assessment

ASA (aspirin) is a commonly used non-prescription drug for the treatment of pain, fever and inflammation. It is also widely used in low doses in the prevention for cardiovascular disease. The use of ASA in cosmetics is almost non-existent. In Europe, there is no existing regulation, whereas the use of ASA in cosmetic products is prohibited in Canada. There are some aspects that need to be considered when assessing the safety of ASA in cosmetics:

i) ASA is commonly used and the recommended daily drug dose has the potential to cause unwanted effects. Any additional contribution from cosmetics to the total exposure of ASA may increase the risk of unwanted side-effects, such as gastric mucosal damage which has been

observed in humans at low doses such as 75 mg/day. It has been established that this effect is related to systemic exposure, and thus relevant for cosmetics via the dermal route.

ii) Reproductive malformations and foetal deaths have been reported in animal studies at 75 mg/kg bw ASA and greater. In addition, one epidemiological study suggested an association between the use of ASA during pregnancy and with increased risk of cryptorchidism. This effect was not found in another study. These doses are far higher than the calculated exposure from cosmetics at present time. However, due to the limited data and the severity of the adverse effect, the possible contribution from ASA derived from cosmetic products should not be neglected.

iii) Although there exists divergent opinions in the scientific community with regard to an association between the use of aspirin and the development of Reye syndrome, a possible association has led to a restriction in some countries in Europe for the use of aspirin in children under 16 years old.

The exposure of ASA from cosmetics should be kept at levels which do not cause adverse health effects. As 75 mg/kg/day have been shown to cause gastric mucosal damage in humans, this was used to calculate the LOAEL value (75 mg/day/ 60 kg = 1.25 mg/kg/day). The NOAEL value was obtained by dividing LOAEL by three, yielding a NOAEL of 0.42 mg/kg bw. We estimated the margin of safety (MoS) for two different cosmetic product categories that contain ASA: i) leave-on aftershave cream for men and women and ii) non-spray deodorant. For a nail hardener containing ASA, the dermal contact and exposure was considered to be negligible. Since the NOAEL is based on human data, a MoS of 10 is sufficient as a safety margin.

MoS for overall exposure for ASA from cosmetic products, men: 1.3
MoS for overall exposure for ASA from cosmetic products, women: 0.3

Based on 1 % use levels of ASA in cosmetic products (note that the actual concentrations are unknown), the estimated overall systemic exposure dose (SED) for women is 1.32 mg/kg bw/day. This corresponds to a dose of 79 mg for a 60 kg person, which is exceeding the chronic low-dose level of 75 mg/day ASA shown to cause gastric mucosal damage. Thus, the contribution from cosmetics to the total exposure when ASA is also used as a medicinal drug increases the risk for unwanted side-effects (even at 0.1 % concentration = approx. 8 mg/day). For more accurate estimates of exposure there is need for more information about skin penetration and actual concentrations used in cosmetic products.

As mentioned, ASA is rapidly hydrolyzed to salicylic acid in the body. Salicylic acid is widely used in cosmetics and the overall systemic exposure for salicylic acid from cosmetics is estimated to be 0.56 mg/kg bw. The NOAEL value for salicylic acid was set to 75 mg/kg bw/day (SCCNFP, 2001). Salicylates are also naturally present in food, with daily intake estimated to be 10-200 mg/day. Salicylates are also used in cosmetics and added to food as flavouring agents. Like ASA, other salicylates (salicylic acid and its salts and esters) inhibit the enzyme cyclo-oxygenase, which enters into the production of prostaglandins. However, the potency of salicylates is far less than that for ASA, as it is the acetyl group that is responsible for the irreversible effect on platelets. The effect of salicylates is only temporary. Therefore, it would not be correct to assess the Margin of Safety of the summarized exposure of salicylates from food and cosmetics together with the systemic exposure dose of ASA.

8. Conclusion

We propose to *prohibit* the use of ASA in *all cosmetic products.* The estimated margin of safety (MoS = 0.3) is markedly below MoS=10, which is considered to be sufficient when NOAEL is based on human data. Thus, potential adverse effects of ASA as it relates to cosmetics per se, and/or due to the total exposure from cosmetics and pharmaceuticals, cannot be disregarded.

9. References

Antiplatelet Trialists' Collaboration Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients.. BMJ. 1994 Jan 8;308(6921):81-106.

Berger JS, Brown DL, Becker RC. Low-dose aspirin in patients with stable cardiovascular disease: a meta-analysis. Am J Med. 2008 Jan;121(1):43-9.

Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. JAMA. 2007 May 9;297(18):2018-24.

Chowdhury A, Ganguly G, Chowdhury D, Santra A, Gupta JD, Roy T. Gastro-duodenal mucosal changes associated with low-dose aspirin therapy: a prospective, endoscopic study. Indian J Gastroenterol. 2001 Nov-Dec;20(6):227-9.

Cryer B, Kliewer D, Sie H, McAllister L, Feldman M. Effects of cutaneous aspirin on the human stomach and duodenum. Proc Assoc Am Physicians. 1999 Sep-Oct;111(5):448-56.

Davies NM, Wallace JL. Nonsteroidal anti-inflammatory drug-induced gastrointestinal toxicity: new insights into an old problem. J Gastroenterol. 1997 Feb;32(1):127-33.

Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. BMJ. 2000 Nov 11;321(7270):1183-7.

de Abajo FJ, García Rodríguez LA. Risk of upper gastrointestinal bleeding and perforation associated with low-dose aspirin as plain and enteric-coated formulations. BMC Clin Pharmacol. 2001;1:1.

Done AK. Salicylate intoxication. Significance of measurements of salicylate in blood in cases of acute ingestion. Pediatrics. 1960 Nov;26:800-7.

Fortun PJ, Hawkey CJ. Nonsteroidal antiinflammatory drugs and the small intestine. Curr Opin Gastroenterol. 2007 Mar;23(2):134-41.

Fox K, Garcia MA, Ardissino D, et al. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J. 2006 Jun;27(11):1341-81.

Garcia Rodriguez LA, Hernandez-Diaz S, de Abajo FJ. Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. Br J Clin Pharmacol. 2001 Nov;52(5):563-71.

Hill JB. Salicylate intoxication. N Engl J Med. 1973 May 24;288(21):1110-3.

Jensen MS, Rebordosa C, Thulstrup AM, Toft G, Sørensen HT, Bonde JP, Henriksen TB, Olsen J. Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy and risk of cryptorchidism. Epidemiology. 2010 Nov;21(6):779-85.

Kawachi T, Yahagi T, Kada T, Tazima Y, Ishidate M, Sasaki M, Sugiyama T. Cooperative programme on short-term assays for carcinogenicity in Japan. IARC Sci Publ. 1980;(27):323-30.

Kelly JP, Kaufman DW, Jurgelon JM, et al. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. Lancet. 1996 Nov 23;348(9039):1413-6.

King MT, Beikirch H, Eckhardt K, Gocke E, Wild D. Mutagenicity studies with x-ray-contrast media, analgesics, antipyretics, antirheumatics and some other pharmaceutical drugs in bacterial, Drosophila and mammalian test systems. Mutat Res. 1979 Jan;66(1):33-43.

Kristensen DM, Hass U, Lesné L, Lottrup G, Jacobsen PR, Desdoits-Lethimonier C, Boberg J, Petersen JH, Toppari J, Jensen TK, Brunak S, Skakkebaek NE, Nellemann C, Main KM, Jégou B, Leffers H. Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat. Hum Reprod. 2011 Jan;26(1):235-44.

Levy G, Tsuchiya T. Salicylate accumulation kinetics in man. N Engl J Med. 1972 Aug 31;287(9):430-2.

Macdonald S. Aspirin use to be banned in under 16 year olds. BMJ. 2002 Nov 2;325(7371):988. PubMed PMID: 12411346; PubMed Central PMCID: PMC1169585.

Morra P, Bartle WR, Walker SE, Lee SN, Bowles SK, Reeves RA. Serum concentrations of salicylic acid following topically applied salicylate derivatives. Ann Pharmacother. 1996 Sep;30(9):935-40.

Nakatsuka T and Fujii T. Comparative teratogenicity study of diflunisal and aspirin in the rat. Oyo Yakuri, 1979, 17: 551-557.

Odashima S. Cooperative programme on long-term assays for carcinogenicity in Japan. IARC Sci Publ. 1980;(27):315-22.

Prichard PJ, Kitchingman GK, Walt RP, Daneshmend TK, Hawkey CJ. Human gastric mucosal bleeding induced by low dose aspirin, but not warfarin. BMJ. 1989 February 25; 298(6672): 493–496)

Procter & Gamble. Acute percutaneous toxicity in rabbits, ECM BTS 206, 1976b.

Procter & Gamble. Perinatal toxicity study in rats, BCS0062(S2), 1994e.

Roberts MS, Favretto WA, Meyer A, Reckmann M, Wongseelashote T. Topical bioavailability of methyl salicylate. Aust N Z J Med. 1982 Jun;12(3):303-5.

Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, Meade TW. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet. 2010 Nov 20;376(9754):1741-50.

Sarah Macdonald. Aspirin use to be banned in under 16 year olds. BMJ. 2002 November 2; 325(7371): 988.

SCCNFP. Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products indented for consumers concerning salicylic acid. 2001.

SCCS (Scientific Committee on Consumer Safety). The SCCS's Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation, 7th revision. 2010.

Shamsher AA, Charoo NA, Kohli K, Pillai K, Rahman Z (2010) Effect of transdermally delivered aspirin on blood coagulation parameters. Am. J. Biomed. Sci. 2010, 2(2), 129-141; doi: 10.5099/aj100200129

Skeljo MV, Giraud AS, Yeomans ND. Gastric mucosal damage induced by nonsalicylate nonsteroidal antiinflammatory drugs in rats is mediated systemically. Dig Dis Sci. 1993 Nov;38(11):2038-42.

Sorensen HT, Mellemkjaer L, Blot WJ, et al. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. Am J Gastroenterol. 2000 Sep;95(9):2218-24.

Swain AR, Dutton SP, Truswell AS. Salicylates in foods. J Am Diet Assoc. 1985 Aug;85(8):950-60.

Tanaka S, Kawashima K, Nakaura S, Nagao S, Kuwamura T, Takanaka A, Omori Y. Studies on teratogenic effects of salicylic acid and aspirin in rats as related to fetal distribution. Congenital Abnormalities. 1973, 13: 73-84.

Trasler DG. Aspirin-induced cleft lip and other malformations in mice. Lancet 1965 Mar 13;1(7385):606-7.

Tuchmann-Duplessis H, Hiss D, Mottot G, Rosner I. Effects of prenatal administration of acetylsalicylic acid in rats. Toxicology. 1975;3(2):207-11.

Wilson JG, Ritter EJ, Scott WJ, Fradkin R. Comparative distribution and embryotoxicity of acetylsalicylic acid in pregnant rats and rhesus monkeys. Toxicol Appl Pharmacol. 1977 Jul;41(1):67-78.

Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med. 1999 Jun 17;340(24):1888-99.

Yeomans ND, Hawkey CJ, Brailsford W, Naesdal J. Gastroduodenal toxicity of low-dose acetylsalicylic acid: a comparison with non-steroidal anti-inflammatory drugs. Curr Med Res Opin. 2009 Nov;25(11):2785-93.

Online:

Codecheck © 2011. Available at: http://www.codecheck.info/ (accessed 19th September 2011).

CosIng, European Commission, Health and Consumers, Cosmetics. Available at: http://ec.europa.eu/consumers/cosmetics/cosing/) (accessed 3th October 2011).
EWG's Skin Deep © Cosmetic Safety Database. Environmental Working group. Available at: http://www.ewg.org/skindeep/ (accessed 27th October 2011).

Health Canada, Government of Canada. Available at: http://www.hc-sc.gc.ca/index-eng.php (accessed 4th October 2011).

IPCS. International Programme on Chemical Safety. Available at: http://www.inchem.org/documents/icsc/icsc/eics0822.htm (accessed 20th September 2011).

Norsk Legemiddelhåndbok, Paracetamol. Available at: http://www.legemiddelhandboka.no/xml/) (accessed 19th September 2011).

Norwegian Medicines Agency, Aspirin. Available at: http://legemiddelverket.no/custom/Preparatsok/prepSearch____80333.aspx?mainSearch=cyklokapron&onlyheading (accessed 19th September 2011).

The product called "**3200 Redness Relief Treatment»** is advertised on the internet 16 may 2013 at: http://www.paulaschoice.com.au/Members--Sale-Page-(1)/Skin-Relief-Treatment-(1).aspx#

10. Annexes

Annex 2:

Skin penetration data - Edetox database

Search In Vitro Studies Side 1 av 1

Average (Mean) Results for Acetylsalicylic Acid with All Species Skin

Lag Time	Kp	Flux
	0.00365	

8 In Vitro Records Found for Acetylsalicylic Acid with All Species Skin, All Cells

Search Again Print

Chemical	Study No.	Vehicle	Species	Site	Membrane	Area (cm2)	Cell Type	Exposure Time (h)	Study Length (h)	% Recovery	% Absorbed	s-s-flux (mcrg/cm2/h)	kp (cm/h)	n	Lag Time (h)	Ref.No
Acetylsalicylic Acid	810	Petrolatum	Rat	Back	Full Thickness Skin	1.13	Static				29		6.5E-05	4		101
Acetylsalicylic Acid	1083	Water	Human	Abdomen	Full Thickness Skin	1	Static	72	72				0.00724	3		158
Acetylsalicylic Acid	1189	Acetone	Human	Abdomen	Dermatomed to 0.43mm		Static	48	48		11					175
Acetylsalicylic Acid	1290	Acetone	Mouse	Not Given	Full Thickness Skin	2	Flow-through	5	5	100.9	49.2			3		203
Acetylsalicylic Acid	1297	Acetone	Rat	Not Given	Full Thickness Skin	2	Flow-through	5	5	95.1	6.8			3		203
Acetylsalicylic Acid	1304	Acetone	Mouse	Not Given	Full Thickness Skin	2	Flow-through	5	5	99.2	46.8			2		203
Acetylsalicylic Acid	1310	Acetone	Rat	Not Given	Full Thickness Skin	2	Flow-through	5	5	90.8	4.9			2		203
Acetylsalicylic Acid	1407	Acetone	Rat	Dorsal	Dermatomed to 0.35mm	0.32	Flow-through	24	72	107.6	16.7			6		219

Edetox database – University of Newcastle (http://edetox.ncl.ac.uk/index.html)
8 In Vitro Records Found for Acetylsalicylic Acid with All Species Skin, All Cells. Average (Mean) Results for Acetylsalicylic Acid with All Species Skin.
(http://edetox.ncl.ac.uk/References.aspx?id=219)

References:

Degim IT, Pugh WJ, Hadgraft J. Skin Permeability Data Anomalous Results (1998) Int. J. Pharm., 170:129-133

Giles AL Jr, Bronaugh RL, Stewart RF, Congdon ER. Methods For In Vitro Percutaneous Absorption Studies I. Comparison With In Vivo Studies (1982) Toxicol. Appl. Pharmacol., 62:474-480

Southwell D, Barry BW, Woodford R. Variations In Permeability Of Human Skin Within And Between Specimens (1984) Int. J. Pharm., 18:299-309

Frantz SW, Dittenber DA, Eisenbrandt DL, Watanabe PG. Evaluation Of A Flow Through In Vitro Skin Penetration Chamber Method Using Acetone-Deposited Organic Solids (1990) J. Toxicol.:Cutaneous Ocul. Toxicol., 9:277-299

Miselnicky SR, Lichtin JL, Sakr A, Bronaugh RL. The Influence of Solubility, Protein Binding, and Percutaneous Absorption On Reservoir Formation In The Skin (1988) J. Soc. Cosmet. Chem., 39:169-177

Annex 3: Skin penetration - references

References:

1. Schwarb FP, Gabard B, Rufli T, Surber C. Percutaneous absorption of salicylic acid in man after topical administration of three different formulations. Dermatology. 1999;198(1):44-51. PubMed PMID: 10026401.

2. Levang AK, Zhao K, Singh J. Effect of ethanol/propylene glycol on the in vitro percutaneous absorption of aspirin, biophysical changes and macroscopic barrier properties of the skin. Int J Pharm. 1999 Apr 30;181(2):255-63. PubMed PMID: 10370221.

3. Degim T, Pugh WJ, Hadgraft. Skin permeability data: anomalous results. Int J Pharmaceutics 170: 129-133. 1998

4. McMahon GP, O'Connor SJ, Fitzgerald DJ, le Roy S, Kelly MT. Determination of aspirin and salicylic acid in transdermal perfusates. J Chromatogr B Biomed Sci Appl. 1998 Apr 10;707(1-2):322-7. PubMed PMID: 9613967.

5. Rougier A, Lotte C, Maibach HI. The hairless rat: a relevant animal model to predict in vivo percutaneous absorption in humans? J Invest Dermatol. 1987 May;88(5):577-81. PubMed PMID: 3572028.

6. Gerber M, Breytenbach JC, Hadgraft J, du Plessis J. Synthesis and transdermal properties of acetylsalicylic acid and selected esters. Int J Pharm. 2006 Mar 9;310(1-2):31-6. Epub 2006 Jan 26. PubMed PMID: 16442756.

7. Waters LJ, Shahzad Y, Stephenson J. Modelling skin permeability with micellar liquid chromatography. Eur J Pharm Sci. 2013 Aug 13;50(3-4):335-340. doi: 10.1016/j.ejps.2013.08.002. [Epub ahead of print] PubMed PMID: 23948555.

8. Shamsher AA, Charoo NA, Kohli K, Pillai K, Rahman Z. Effect of transdermally delivered aspirin on blood coagulation parameters. Am. J. Biomed. Sci. 2010, 2(2), 129-141; doi: 10.5099/aj100200129.

Abstracts:

1.
Dermatology. 1999;198(1):44-51.

Percutaneous absorption of salicylic acid in man after topical administration of three different formulations.

Schwarb FP, Gabard B, Rufli T, Surber C.

Department of Dermatology, University Hospital, Basel, Switzerland.

OBJECTIVE: To determine the amount of drug which is absorbed during 1 day following topical application of three different preparations containing salicylic acid.
METHODS: Ten grams of the formulations, either (a) Kerasaltrade mark 5% ointment, (b) salicylic acid 5% or (c) 10% in petrolatum, were administered consecutively to a 600-cm2 area on alternating sides of the back of healthy volunteers (n = 9). Thirty minutes after application, a skin area of 2.54 cm2 was stripped with D-Squametrade mark adhesive disks to determine the amount of salicylic acid in the stratum corneum. The entire application site was then covered by a thin gauze bandage and was not washed for the next 24 h. Urine was collected for 26 h following administration, hydrolyzed and assayed by HPLC analysis.
RESULTS: The absolute amounts absorbed and excreted were 52.6 +/- 29.4 mg (mean

+/- SD), 127.1 +/- 43.9 mg and 208.0 +/- 81.7 mg, and the doses absorbed in relation to the doses applied (500 mg salicylic acid in case of formulations a and b and 1,000 mg for formulation c) were 9.3 +/- 3.8, 25.1 +/- 8.5 and 20.2 +/- 7.7%, respectively. The amounts of salicylic acid in the skin 30 min after application were 36.3 +/- 16.5, 18.2 +/- 11.9 and 31.3 +/- 15.4 microg/ cm2 as determined by the tape stripping procedure.
CONCLUSIONS: Significant differences in the doses absorbed were detected between the two formulations a and b (same concentration) with different vehicles (p value < 0.001) as well as between b and c (same vehicle) with different concentrations (p value = 0.018) using Student's paired t test. These results demonstrate that salicylic acid is well absorbed by healthy skin.

PMID: 10026401 [PubMed - indexed for MEDLINE]

2.
Int J Pharm. 1999 Apr 30;181(2):255-63.

Effect of ethanol/propylene glycol on the in vitro percutaneous absorption of aspirin, biophysical changes and macroscopic barrier properties of the skin.

Levang AK, Zhao K, Singh J.

Department of Pharmaceutical Sciences, College of Pharmacy, North Dakota State University, Fargo, ND 58105, USA.

The effect of the solvent systems ethanol (EtOH), propylene glycol (PG) and combinations thereof was examined on the in vitro percutaneous absorption of the antithrombotic, aspirin, through porcine epidermis. Biophysical changes in the stratum corneum lipids were studied through the use of Fourier transform infrared (FTIR) spectroscopy. Macroscopic barrier properties of the epidermis were examined through the use of in vitro transepidermal water loss (TEWL). The flux of aspirin increased with increasing concentrations of EtOH in the solvent systems. The maximum flux of aspirin was achieved by 80% EtOH in combination with 20% PG beyond which (i.e. 100% EtOH) there was no increase in the flux. FTIR spectroscopic study was enacted in order to determine the biophysical properties of the stratum corneum when the solvents were applied. The FTIR spectra of the stratum corneum treated with 80% EtOH/20% PG showed a maximum decrease in absorbance for the asymmetric and symmetric C&z. sbnd;H peaks, which suggests a greater loss of the lipids in the stratum corneum layers. In vitro TEWL studies allowed an investigation into the macroscopic barrier integrity properties of the stratum corneum. The TEWL results indicated that each of the solvent systems significantly enhanced (P<0.05) in vitro TEWL in comparison to the control. In conclusion, 80% EtOH/20% PG enhanced the percutaneous absorption of aspirin by perturbing the macroscopic barrier integrity of the stratum corneum and through a loss of stratum corneum lipids.

3.

Abstract

Analysis of published skin permeation data has shown that a few compounds appear to have anomalous skin permeability coefficients. These include penetrants such as naproxen, atropine and nicotine. The permeabilities of these materials were re-determined together with aspirin, benzoic acid, diclofenac, ibuprofen and methyl nicotinate. The results are discussed in conjunction with published regression analyses and compared with values predicted by estimating the octanol–water partition coefficients using commercial software packages.

Keywords: Skin permeability; Prediction; Transdermal; Skin absorption

4.
J Chromatogr B Biomed Sci Appl. 1998 Apr 10;707(1-2):322-7.

Determination of aspirin and salicylic acid in transdermal perfusates.

McMahon GP, O'Connor SJ, Fitzgerald DJ, le Roy S, Kelly MT.

Department of Chemistry, The Royal College of Surgeons in Ireland, St. Stephen's Green, Dublin.

A high-performance liquid chromatographic (HPLC) method has been developed for the simultaneous determination of aspirin and salicylic acid in transdermal perfusates. The compounds were separated on a C8 Nucleosil column (5 microm, 250x4.6 mm) using a mobile phase containing a mixture of water-acetonitrile-orthophosphoric acid (650:350:2, v/v/v) and a flow-rate of 1 ml/min. The transdermal samples were in phosphate-buffered saline (PBS) and could be injected directly onto the HPLC system. The method was reproducible with inter-day R.S.D. values of no greater than 3.46 and 2.60% for aspirin and salicylic acid, respectively. The method was linear over the concentration range 0.2-5.0 microg/ml and had a limit of detection of 0.05 microg/ml for both compounds. For certain samples, it was necessary to ensure that no transmembrane leakage of the aspirin prodrugs had occurred. In these cases, a gradient was introduced by increasing the acetonitrile content of the mobile phase after the salicylic acid had eluted. The method has been applied to the determination of aspirin and salicylic acid in PBS following in vitro application of the compounds to mouse skin samples.

PMID: 9613967 [PubMed - indexed for MEDLINE]

5.
J Invest Dermatol. 1987 May;88(5):577-81.

The hairless rat: a relevant animal model to predict in vivo percutaneous absorption in humans?

Rougier A, Lotte C, Maibach HI.

Percutaneous absorption of 4 radiolabeled molecules was compared in the hairless rat (back) and in different anatomic sites in human (arm, abdomen, postauricular, forehead). The conditions under which these 4 compounds were administered (area treated, dose, vehicle, contact time, etc.) were similar in both species. The results showed that, in humans and rats, there exists the same rank order in total absorption: benzoic acid sodium salt less than caffeine less than benzoic acid less than acetylsalicylic acid. In both species there was a factor of 3 between the most and the least absorbed molecule. Although skin permeability varied significantly with the physicochemical nature of the compound administered, it also depended on the anatomic site involved. Independent of the molecule studied, the rank order of permeability of the sites tested in humans appeared as follows: arm less than or equal to abdomen less than postauricular less than forehead. There was a factor of 3 between the most and the least permeable sites. For each molecule and each anatomic site, the ratios of total percutaneous absorption human/hairless rat (back) were determined. For a given anatomic site and whatever the molecule tested, these ratios were constant. It thus appears that when conditions are carefully controlled, it may be possible, by measurements on animals, to predict the absorption of a compound in humans. Further experimentation with chemicals of varied physicochemical properties will be required for validation of the model.

PMID: 3572028 [PubMed - indexed for MEDLINE]

6.
Int J Pharm. 2006 Mar 9;310(1-2):31-6. Epub 2006 Jan 26.

Synthesis and transdermal properties of acetylsalicylic acid and selected esters.

Gerber M, Breytenbach JC, Hadgraft J, du Plessis J.

Pharmaceutical Chemistry, School of Pharmacy, North-West University, Potchefstroom 2520, South Africa. fchmg@puknet.puk.ac.za

The primary aim of this study was to determine the transdermal penetration of acetylsalicylic acid and some of its derivatives, to establish a correlation, if any, with selected physicochemical properties and to determine if transdermal application of acetylsalicylic acid and its derivatives will give therapeutic drug concentrations with respect to transdermal flux. Ten derivatives of acetylsalicylic acid were prepared by esterification of acetylsalicyloyl chloride with ten different alcohols. The experimental aqueous solubility, logD and transdermal flux values were determined for acetylsalicylic acid and its derivatives at pH 4.5. In vitro penetration was measured through excised female human abdominal skin in diffusion cells. The experimental aqueous solubility of acetylsalicylic acid (6.56 mg/ml) was higher than that of the synthesised acetylsalicylate derivatives (ranging from 1.76 x 10(-3) to 3.32 mg/ml), and the logD of acetylsalicylic acid (-0.85) was lower than that of its derivatives (ranging from -0.25 to 1.95). There was thus an inverse correlation between the aqueous solubility data and the logD values. The experimental transdermal flux of acetylsalicylic acid (263.83 nmol/cm(2)h) was much higher than that of its derivatives (ranging from 0.12 to 136.02 nmol/cm(2)h).

PMID: 16442756 [PubMed - indexed for MEDLINE]

7.
Eur J Pharm Sci. 2013 Aug 13;50(3-4):335-340. doi: 10.1016/j.ejps.2013.08.002. [Epub ahead of print]

Modelling skin permeability with micellar liquid chromatography.

Waters LJ, Shahzad Y, Stephenson J.

School of Applied Sciences, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, UK. Electronic address: l.waters@hud.ac.uk.

This study evaluates the potential application of micellar liquid chromatography (MLC) to predict skin permeation with a series of model compounds. MLC has previously been found to be useful in the prediction of partition coefficient values (logP) for pharmaceutical compounds, yet has not been incorporated in skin permeability models prior to this work. This article provides statistically supported data that this technique enhances the ability to predict the permeability of similar drugs through the skin (Kp). The replacement of a traditional physicochemical parameter, namely the octanol-water partition coefficient (logPow) with a chromatographically determined value (logPmw), results in a quantitative partition-permeability relationship that is robust to variation. MLC offers many benefits compared with the traditional techniques employed to obtain logP values.

PMID: 23948555 [PubMed - as supplied by publisher]

8.

Effect of Transdermally Delivered Aspirin on Blood Coagulation Parameters

Areeg A. Shamsher*, Naseem A. Charoo, Kanchan Kohli, Krishna Pillai, Ziyaur Rahman

Faculty of Pharmacy, Jamia Hamdard University, New Delhi-110062, India
***Corresponding author**
(Author is presently affiliated to following University)
Department of Pharmacology,
Khartoum College of Medical Sciences,
Aljerief West, Ist Block Number 398
P.O. Box 10995
Khartoum, Sudan
E-mail: areeg102@yahoo.co.in

Received: 2 July 2009; | Revised: 16 August 2009; | Accepted: 15 December 2009

Abstract

The efficacy of oral aspirin treatment in the secondary prevention of cardio and cerebro vascular disease is well known. However oral administration is often associated with abdominal discomfort. The feasibility of delivering aspirin transdermally from eudragit and polyvinyl acetate (PVA) matrix-type patches to enhance its antithrombotic efficiency of aspirin was investigated. Transdermal films containing mixture of eudragit RL: eudragit RS and polyvinyl acetate were fabricated. Eudragit RL: eudragit RS (5:1) films containing 30 mg/ transdermal patch aspirin showed maximum release (11.89±1.1μg/cm^2) after 24 hrs as compared to PVA films. With regards to appearance eudragit films were also wrinkle free, uniform, flexible and transparent with good adhesion property to skin. The effect of turpentine oil and lemon oil at different concentrations on the in vitro percutaneous absorption of aspirin from eudragit copolymer patches through rat skin was investigated. Two formulation containing 50 mg/transdermal patch ASA with 0.042 ml turpentine oil and 0.042 ml lemon oil showed a significantly higher flux of ASA 4.22 μg/cm^2/hr and 38.52 μg/cm^2/hr respectively. The optimized formulations influenced the blood coagulation parameters (bleeding time, prothrombin time, Activated partial prothrombin time) significantly by means of affecting both the extrinsic coagulation system and the intrinsic coagulation system as compared to orally administered and control gel formulations.

Keywords: Transdermal; Aspirin; Penetration enhancers; Antiplatelet.

Annex 4

Calculation of the lower therapeutic dose (analgesic and antipyretic effect):

- Lowest drug blood plasma concentration that yield a therapeutic effect: 10 mg/dL = 100 mg/L
- V_D: 0.1 L/kg

V_D = Total amount of drug in the body / Drug blood plasma concentration

Total amount of drug in the body = V_D x Drug blood plasma concentration
= 0.1 L/kg x 100 mg/L
= **10 mg/kg**

Calculation of skin surface for the aftershave cream (based on "the rule of nine")
The aftershave cream can be used on all shaved areas, such as shaved legs.

Skin surface area, women:
The rule of nine is a way to calculate the percentage of the body surface that is affected and is often used to calculate the burn percentage. Each leg constitutes 18% (front = 9%, back = 9%).

½ of each leg: (18+18 %)/2 = 18 %
Skin surface area: 17,500 cm^2 (total body surface) x 0.18 = **3,150 cm^2**

Skin surface area, men:
Skin surface area (SCCS, default value): **305 cm^2**