Enhanced bioavailability of skin whitening actives in topical applications

Contents

Objective

To understand different strategies used for enhancing the bioavailability of skin whitening agents in topical applications by various companies.

Scope

- This report is restricted to four major players in this technology area- Kao, L'Oreal, P&G and Shiseido.
- We have taken patents as a source of information to understand different methods for enhancing bioavailability.

Search methodology

Search strategy	1. Various keywords were retrieved for conducting the search related to enhanced bioavailability of active ingredients in topical applications for skin whitening from pubmed MESH, relevant patents, scientific articles and thesaurus.
	2.Various Class-codes have been retrieved from relevant patents and their citations. Also . (Refer section 4).
	3.The database used for patent search is Thomson innovation.
Keywords	Whitening, lightening, topical, depigmentation, bioavailability, penetration enhancer etc.

Introduction

Skin whitening/lightening/brightening is an important skin care need, especially in the asian population. Whitening skin care is a process in which the darker skin is prepared to look lighter. Human skin color determined from the outermost layer of the skin, the epidermis where the pigment-producing cells melanocytes are localized to produce melanin. The amount of melanin synthesized by the melanocyte, and its distribution pattern in the surrounding keratinocytes, determines the actual color of the skin. Melanin forms through a series of oxidative reactions involving the amino acid tyrosine in the presence of the enzyme tyrosinase.Parvez et al,2006

Elimination of melanin can be done in three ways:

- Suppressing Tyrosinase formation
- Inhibiting Tyrosinase activity
- Reduction of Melanin

Hydroquinone and hydroxyanisole, in the past, were the standard ingredient for skin lightening treatments. However with reports of potential mutagenicity, there has been an increasing impetus to find alternative herbal and pharmaceutical depigmenting agents.

Current trends in skin whitening ingredients

Great advances have been made to understand pigment biology and the processes underlying skin pigmentation in the last decade. Many researchers have begun to produce natural alternatives which mimic the skin lightening properties of hydroquinone and hydroxyanisole. Ingredients such as kojic acid and licorice have become quite popular along with more advanced ingredients like Alpha-Arbutin. When combined, these ingredients can often produce better results that even surpass hydroquinone but without the associated risks. Below is the list of commonly used ingredients that are widely used for skin whitening.

Skin-Lightening Ingredient	*In Vitro* studies	*In Vivo* studies
Hydroquinone	Inhibition of tyrosinase activity and melanin inhibition [128] and inhibition of cellular metabolism by affecting both DNA and RNA syntheses [61].	Clinical studies in patients with melasma shows re pigmentation [54, 55].
Arbutin/deoxyarbutin	Inhibition of tyrosinase activity and melanin production [129], [66]. Inhibition of tyrosine hydroxylase and DOPAoxidase activities [130].	Clinical trial showed overall skin lightness and impr lentigines after 12 -week treatment [70].
Kojic Acid/Kojic acid tripeptides	Inhibition of catecholase activity of tyrosinase [74]. Comparative studies with kojic acid-tripeptides and unconjugated kojic acid [75].	Comparative study on skin-lightening effect of hyd kojic acid showed similar effects [131].
Azelaic acid	Melanin inhibition in melanoma cells [132].	Clinical study on patients with facial hyperpigmenta improvement in pigment intensity by one or mo Comparative study showed 20% azelaic acid is mo 2% hydroquinone in patients with melasma [128]
Aloesin	Inhibition of tyrosinase, tyrosine hydroxylase and DOPA oxidase activities. Also synergistic action with arbutin shown [78, 134].	Clinical study showed suppressed pigmentation by forearm [135].
Resveratrol	Reduction in MITF and tyrosinase promoter activities (transfection studies in melanoma cells) [79, 136].	No trials in humans. Dark-skinned Yucatan swine resveratrol showed visible skin lightening, which histologically [79]
Glabiridin (Liquirice)	Glabrene and isoliquiritigenin in the licorice extract can inhibit both mono- and diphenolase tyrosinase activities [81]	Trial for melasma treatment using liquritin cream s excellent results in 90% of the patients [137]
Soyabean	Soyabean inhibits protease-activated receptor 2 cleavage, affects cytoskeletal and cell surface organization, and reduces keratino cyte phagocytosis [88]	Study on facial photodamage showed that soyabe efficient than the vehicle in improving mottled pig
Niacinamide	No catalytic activity of mushroom tyrosinase or on melanogenesis in monocultures of melanocytes. 35–68% inhibition of melanosome transfer in the coculture model [91]	Clinical study showed significant improvements ve end points: fine lines/wrinkles, hyperpigmentation and red blotchiness [92]
α-Hydroxyacid	Glycolic acid and lactic acid inhibited melanin formation in human melanoma cells. Tyrosinase activity was inhibited. No effect on tyrosinase, TRP-1 and TRP-2 mRNA [98]	Study on topical application of a 10% glycolic acid showed improvement in 91% of patients [138]. Comparative study with hydroquinone showed that not more efficient that hydroquinone [139]
Retinoic acid	Inhibition of tyrosinase/TRP-1 protein expression concomitant with melanin synthesis [99]	Study on overall skin lightening in face showed ligh in 68% of the patients [140]. Clinical trial on melasma showed only marginal sig reduction compared to vehicle [141]
Vitamin C (magnesium ascorbyl phosphate)	Suppression of melanin formation on purified tyrosinase and in melanocytes [108]	Clinical study using magnesium-L-ascorbyl-2-phos resulted in lightening effect in 19 of 34 patients w senile freckles [108]
octadecenedioic acid	Reduction in tyrosinase mRNA and protein expression concomitant with inhibition of melanogenesis [101]	Studies on octadecenedioic acid resulted in a more and overall lighter skin colour [102, 142]

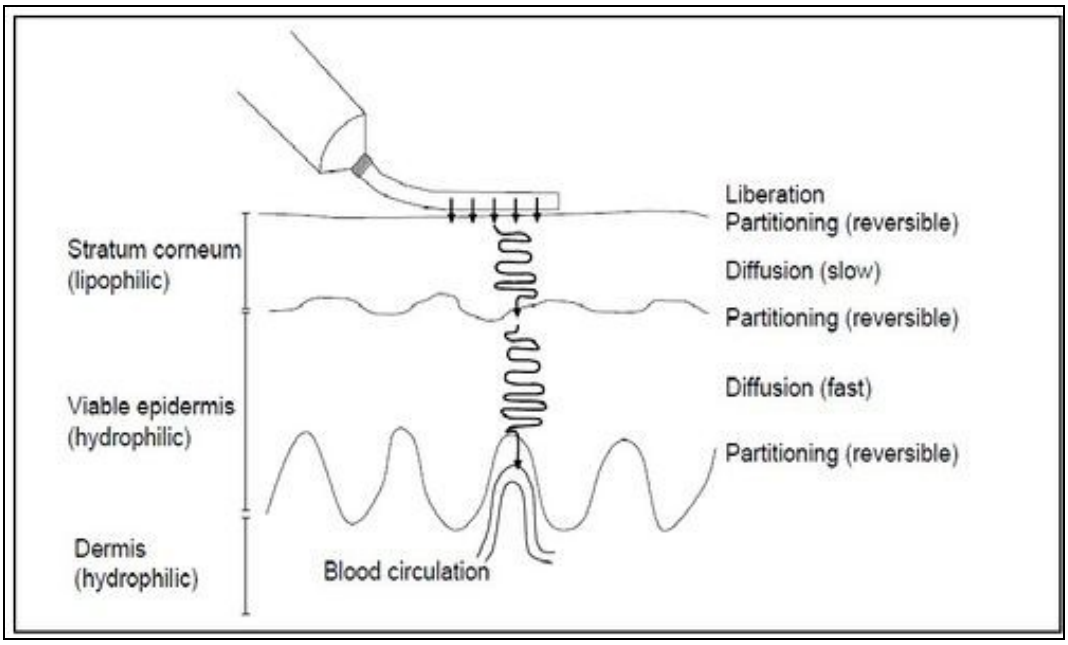
Gillbro & Olsson,2011

- Because of the accessibility and large area of the skin, it has long been considered as promising route for the administration of drugs, where dermal, regional, or systemic effects are desired. The advantages of the topical route of drug administration include: avoidance of the risks and inconvenience of parenteral treatment; avoidance of the variable absorption and metabolism associated with oral treatment; continuity of drug administration, permitting use of pharmacologically active agents with short biological half-lives and potential reduction of gastrointestinal irritation in systemic administration.Deckner et al,1999

- However, the impermeability of skin is well-known, serving as a barrier to ingress of pathogens and toxic chemicals, and egress of physiologic fluids. This impermeability is the result of normal physiologic changes in developing skin,also results in lesser bioavailability.It is already well known that bioavailability of compounds taken topically example skin whitening ingredients are always lesser than that taken orally or intravenously. Bioavailability of topical dosage forms not intended for absorption has proved to be quite difficult, daunting and extremely challenging.

Skin whitening ingredients and enhanced bioavailability

Bioavailability



Schematic depiction of percutaneous absorption,Pellanda(2006)

The determination of the bioavailability of systemically absorbed products is defined as the rate and extent to which the active ingredient or active moiety is absorbed from the drug product and becomes available at the site of action Kanfer and Shargel, 2008. However, when considering products which contain active ingredient(s) not intended for systemic absorption, the US FDA, published the following statement in the US Federal Register (US Federal Register, 2009) where such products?..... may be assessed by (surrogate) measurements intended to reflect the rate and extent to which the active ingredient or moiety becomes available at the site of action?.

Many skin-lightening actives have problems with lesser bioavailability or instability during storage, it also have low affinity to the skin and have little percutaneous absorption. Therefore, several attempts have successfully been made to synthesize conjugates to improve their bioavailabilities. Novel technology has shown great potential for improving the effectiveness and efficiency of delivery of ingredients, e.g.

- Microemulsion- An oil-in-water microemulsion have the ability to encapsulate non polar molecules such as lipids, flavorants, antimicrobials, antioxidants, and vitamins, it formulated using lecithin and an alkyl glucoside. It was proposed as a cosmetic vehicle for arbutin and kojic acid, naturally occurring whitening agents. The stability of these compounds are higher in microemulsion than in aqueous solutions.Gallarate et al,2004
- Liposomes- Liposomes encapsulate water and lipid-soluble pharmacologically and cosmetically active components. Liposomes favor the disposition of encapsulated active ingredients in the epidermis and dermis, while the permeation rate is decreased. This helps to fix active ingredients to the outermost skin layers as desired for cosmetic products.Cevec,1997
- Nanoemulsions- Nanoemulsions are emulsions having small droplet size (20?300nm). They could be used for lipophilic as well as hydrophilic substances with enhanced bioavailability

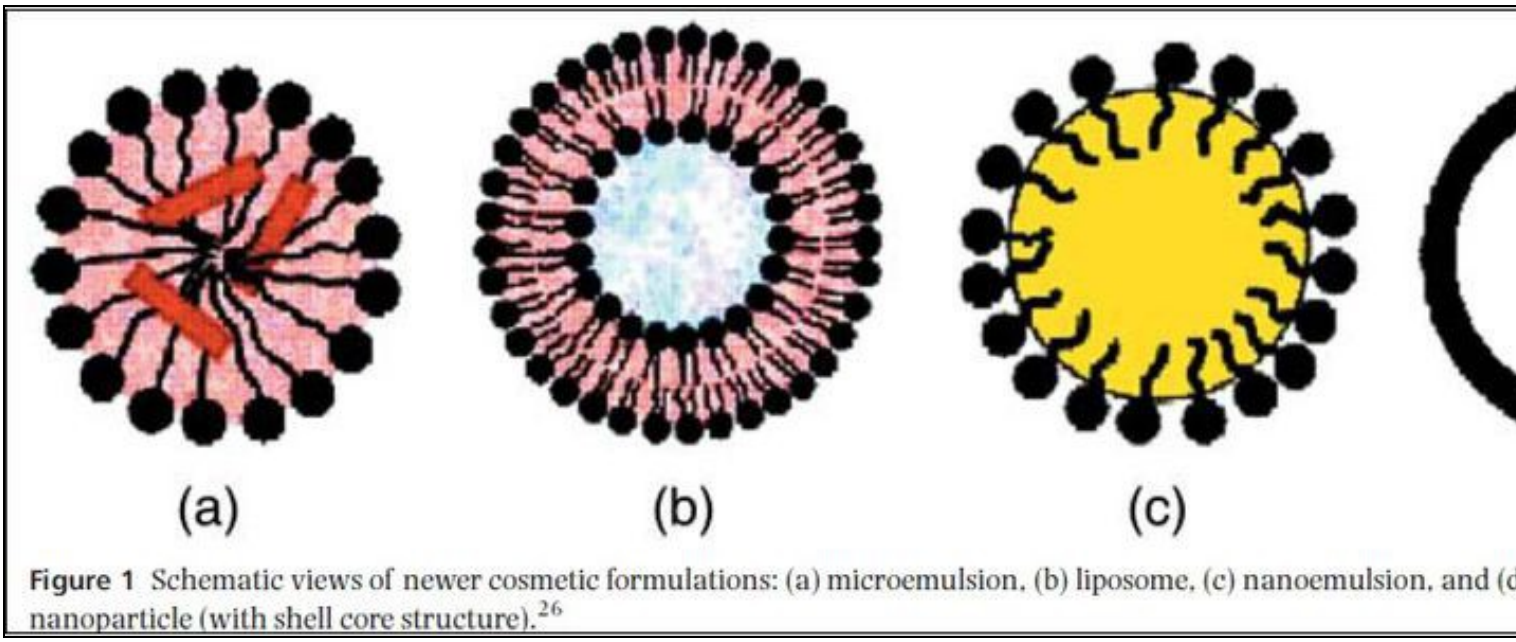


Figure 1 Schematic views of newer cosmetic formulations: (a) microemulsion, (b) liposome, (c) nanoemulsion, and (d) nanoparticle (with shell core structure).[26]

Chanchal & Swarnalata,2008

Researcher also used skin penetration enhancer, volatile silicone and several other organic compound which make the ingredients stable and more bioavailable to the skin.

Concept table

Click here to view concept table

Search strategy

- **Database: Thomson Innovation**
- **Coverage:US Grant, GB App, US App, FR App, WO App, DE Util, EP Grant, DE Grant, EP App, DE App, JP Util, JP Grant, JP App, CN Util, CN App, KR Util , KR Grant, KR App, Other, DWPI**
- **Time Line:1836 - 19 January 2012**

S.No	Concept	Scope	Search strategy	Hits
1	Class codes of skin whitening AND keywords of bioavailability(English)	Full patent spec.	(424062) OR (424449) OR ****	###
2	Class codes of skin whitening AND keywords of bioavailability(German)	Full patent spec.	(A61Q001902) AND (((Bioverfügbarkeit OR ****	###
3	Class codes of skin whitening AND keywords of bioavailability(French)	Full patent spec.	(A61Q001902) AND (((biodisponibilité OR ****	###
4	F terms of skin whitening AND keywords of bioavailability (English)	full spec in japanese only	(4C083EE16) AND ((Bioavailabilit*3 OR ****	###
5	Combined query (Class code of skin whitening and key words of bioavailability)		1 OR 2 OR 3 or 4	###
6	highly relevant class codes of bioavailability and keywords of skin whitening	Claims, Title, Abstract	((514946) OR (514947) OR ****	###
7	Class codes of bioavailability AND key words of skin whitening(English)	Claims title abstract	(5140011) OR (5140022) OR ****	###
8	english keywords and japanese f terms for bioavailability	Claims title abstract	(4C076FF34) OR (4C076FF03) OR ****	###
9	Combined query(Class codes of bio-availability and key words of skin whitening)		6 OR 7 OR 8	###
10	Combined query (key word - classcode search)		5 or 9	###
11	Skin whitening AND bioavailability key words(English)	Claims, Title, Abstract for skin whitening AND Full patent spec. for bioavailability	(((Skin*1 OR*3 derm*2 OR ****	###
12	Class codes of bioavailability AND key words of skin whitening(Geman)	Claims, Title, Abstract for skin whitening AND Full patent spec. for bioavailability	(((Haut OR pelle OR ****	###
13	Class codes of bioavailability AND key words of skin whitening(French)	Claims, Title, Abstract for skin whitening AND Full patent spec. for bioavailability	((((la ADJ2 peau) OR peau OR ****	###
14	Combined query (keyword search)		11 OR 12 OR 13	###
15	Combined query (Kewyword search and keyword - Classcode search)		10 OR 14	###
16	Key words for irrelevant patents	Title, Abstract	(Teeth OR tooth OR****	###
17	Final query		15 NOT 16	###
18	L?Oreal	Assignee Applicant, Assignee/Applicant Standardized, Assignee/ applicant original, Assignee Applicant DWPI and US reassignment	"La Institut Lancome" OR ****	###
19	L?Oreal Restricted		17 AND 18	###
20	Shiseido	Assignee Applicant, Assignee/Applicant Standardized, Assignee/ applicant original, Assignee Applicant DWPI and US reassignment	"SHISEIDO INTERNATIONAL FRANCE" OR ****	###
21	Shiseido Restricted		17 AND 20	###
22	Kao and Kanebo	Assignee Applicant, Assignee/Applicant Standardized, Assignee/ applicant original, Assignee Applicant DWPI and US reassignment	"LABTEC GESELLSCAFT FA?R TECHNOLOGISCHE FORSCHUNG UND ENTTWICKLUNG MBH" OR****	###
23	Kao and kanebo restricted		17 AND 22	###

Relevant class codes and definitions

IPC/ECLA classes

A61	Medical or Veterinary science; Hygiene	Column1	Column2
	A61Q	Use of cosmetics or similar toilet preparation	
		A61Q 19/02	Preparations for care of the skin =>for chemically bleaching or whitening the skin
	****	****	****

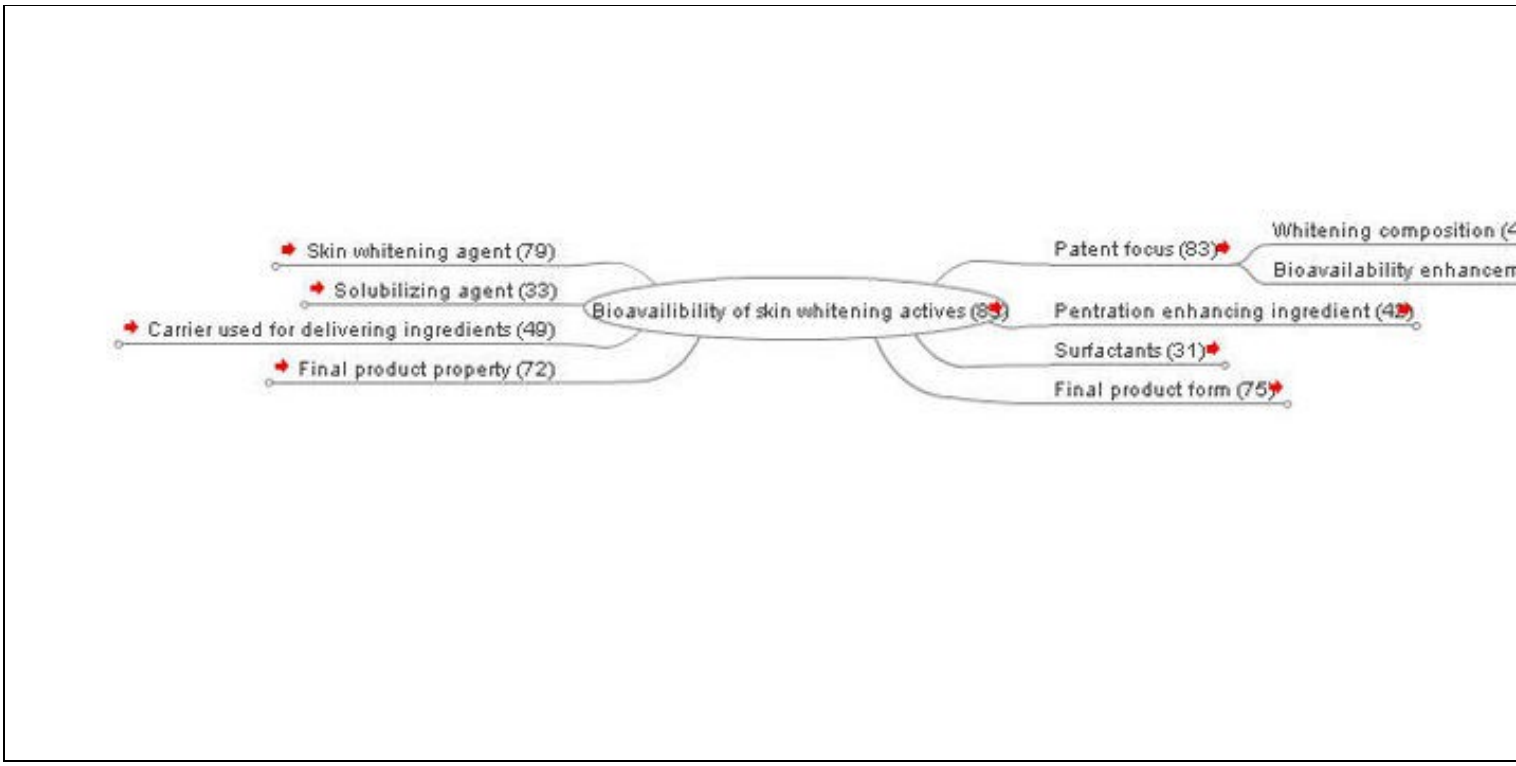
US Classes

424	Drug, bio-affecting and body treating compositions	Column1
	424/62	Bleach for live hair or skin (e.g., peroxides, etc.)
	424/78.03	Topical body preparation containing solid synthetic organic polymer as designated organic active ingredient (doai) => Skin cosmetic coating
	****	****

F-Term

Theme	Title of the theme	F-term	F-term description
4C083	Cosmetics	4C083EE16	Whitening (Tyrosinase inhibition, melanin inhibition)
4C076	Medicinal preparation	4C076FF34	Absorption accelerators or penetrants
****	****	****	****

Taxonomy



Relevant patents

S.No	Patent / Publication No.	Title	Assignee/Applicant	Date of Publication	Problem	Solution
1	US5874095A	Enhanced skin penetration system for improved topical	Richardson Vicks Inc.	2/23/1999	Poor penetration of many drugs across the epidermal lipid barrier	Composition containing a pharmaceutical active(hydroquinone,

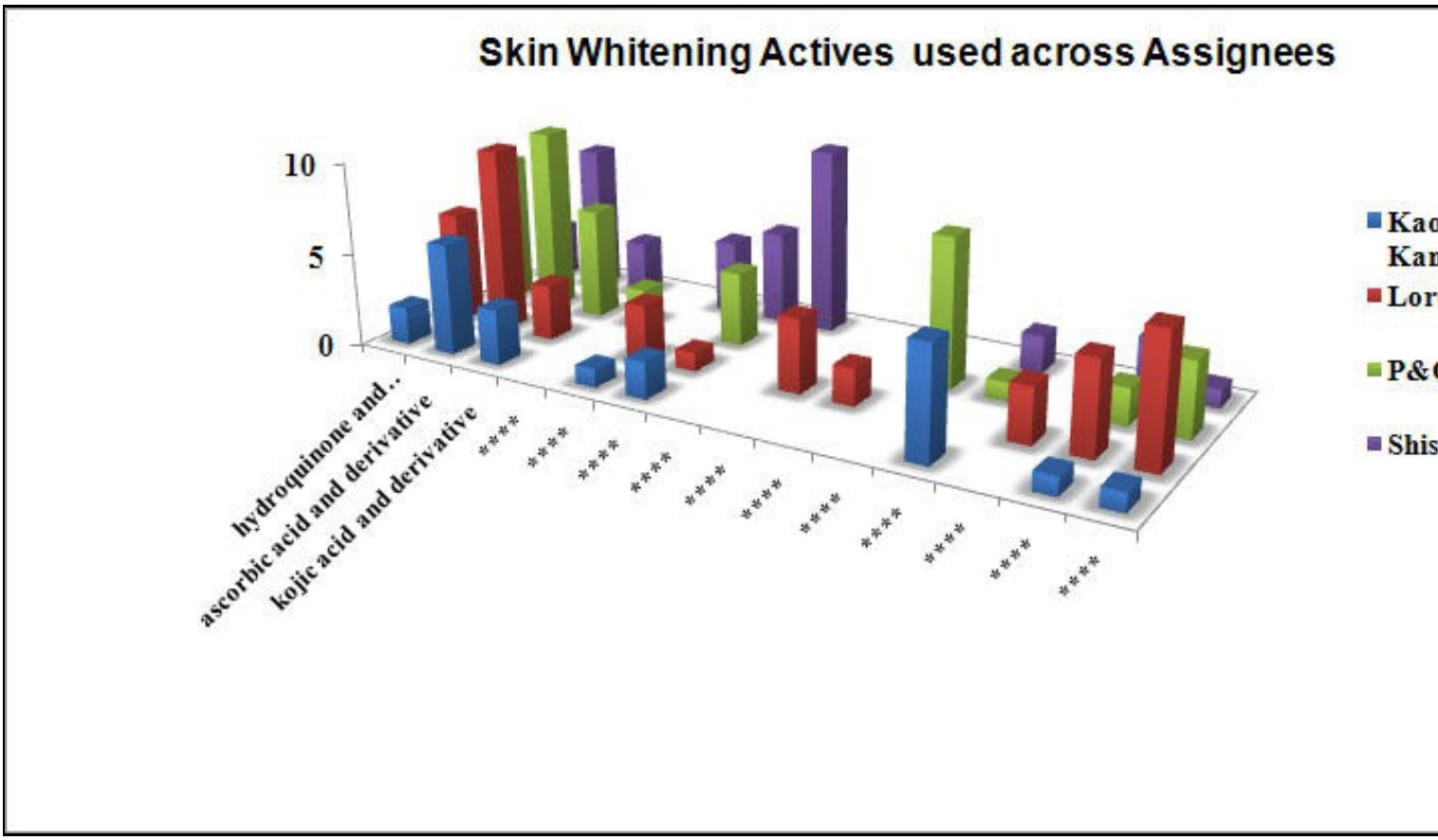
		delivery of drugs			has, until now, frustrated attempts to deliver clinically significant doses of many drugs by the topical route. Compositions provides containing a skin penetration enhancing vehicle with insufficient transdermal penetration Orally administered drugs can increase the dosage required to achieve therapeutic levels and thereby increase undesirable side effects	ascorbic acid, kojic acid and sodium metabisulfite)and polyacrylamide which enhances the skin penetration of drugs. Provide sufficient skin penetration enhancement to achieve therapeutic levels of the drugs in target internal tissues.Compositions with low dermal irritation, especially in compositions requiring a low pH. Compositions having good stability.
2	US20090162305A1	Formulations of low oil content comprising diphenylmethane derivatives	Symrise GmbH & Co. KG	6/25/2009	Sensitive to oxidation and can be stabilized in cosmetic formulations only with difficulty, inadequate action on the skin, high sensitizing potential and causes contact allergies,no reference having a defined content of an oily phase is to be found with less bioavailability	Novel specific (cosmetic) formulations for improving the bioavailability and activity of skin- or hair-lightening agent as diphenylmethane derivatives (tyrosinase inhibitors) commmonly known as styrylresorcinol which has more stbility and little toxicity.
3	*****	****	****	****	****	****

Analysis

Click here to download sample analysis sheet

Trends and Insights

Assigneewise preferred skin whitening actives

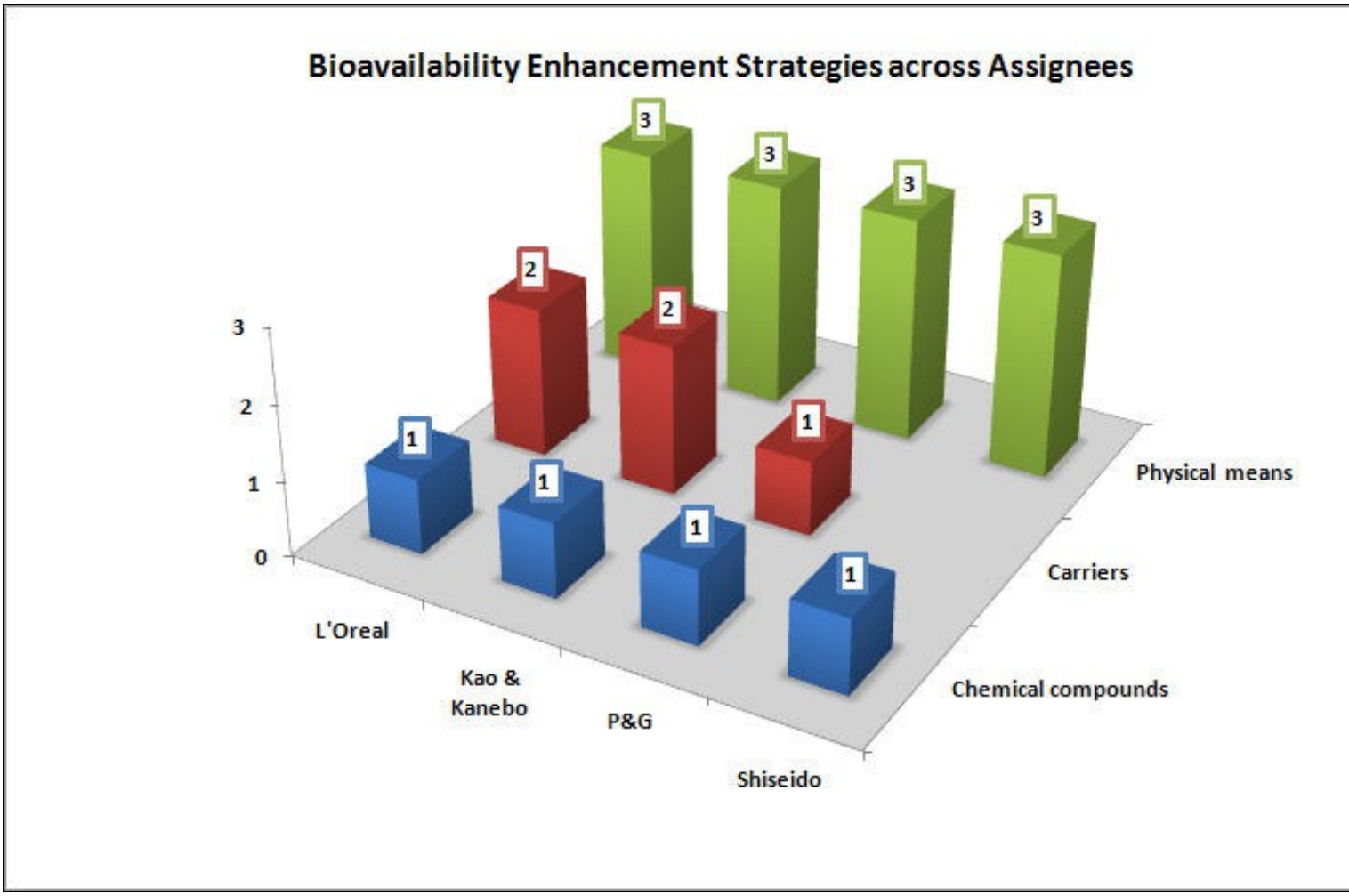


Skin-whitening actives vs Assignees

Key Points

- Tranexamic acid and derivatives are restricted to Shisheido
- Alpha Hydroxy acid and Tocopherol derivatives are restricted to Loreal
- Vitamin B3 and derivatives are exclusive to P&G
- Loreal exclusively exploits biomolecules such as siRNA and Enzymes in whitening compositions
- P & G uses a novel sodium metabisulfite as skin whitening agent
- Kao and Kanebo prefers natural extract as whitening actives

Assignee-wise adopted bioavailability enhancing strategies

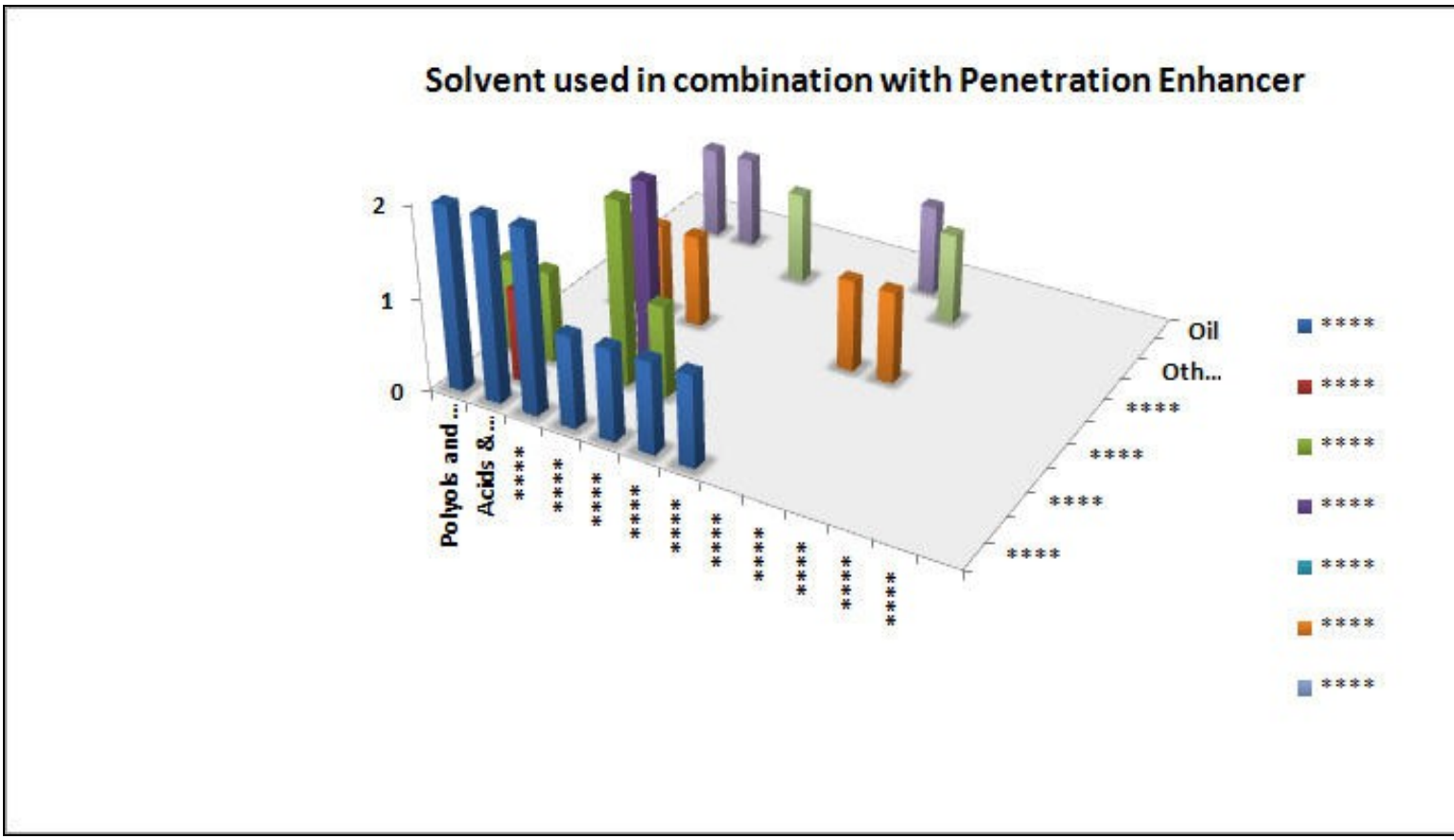


Bioavailability enhancing strategies vs Assignees

Key Points

- Shiseido prefers chemical compounds as penetration enhancers such as silicone compounds, carboxylic acids, etc.
- L?Oreal?s penetration enhancers are mostly carriers such as liposomes, nanoemulsions, etc. followed by physical methods like iontophoresis, ultrasonic waves etc.
- P & G has a preference for carriers followed by physical methods and chemical compounds

Preferred solvent with respect to penetration enhancer



Penetration enhancer (x-axis) vs solvent (z-axis)

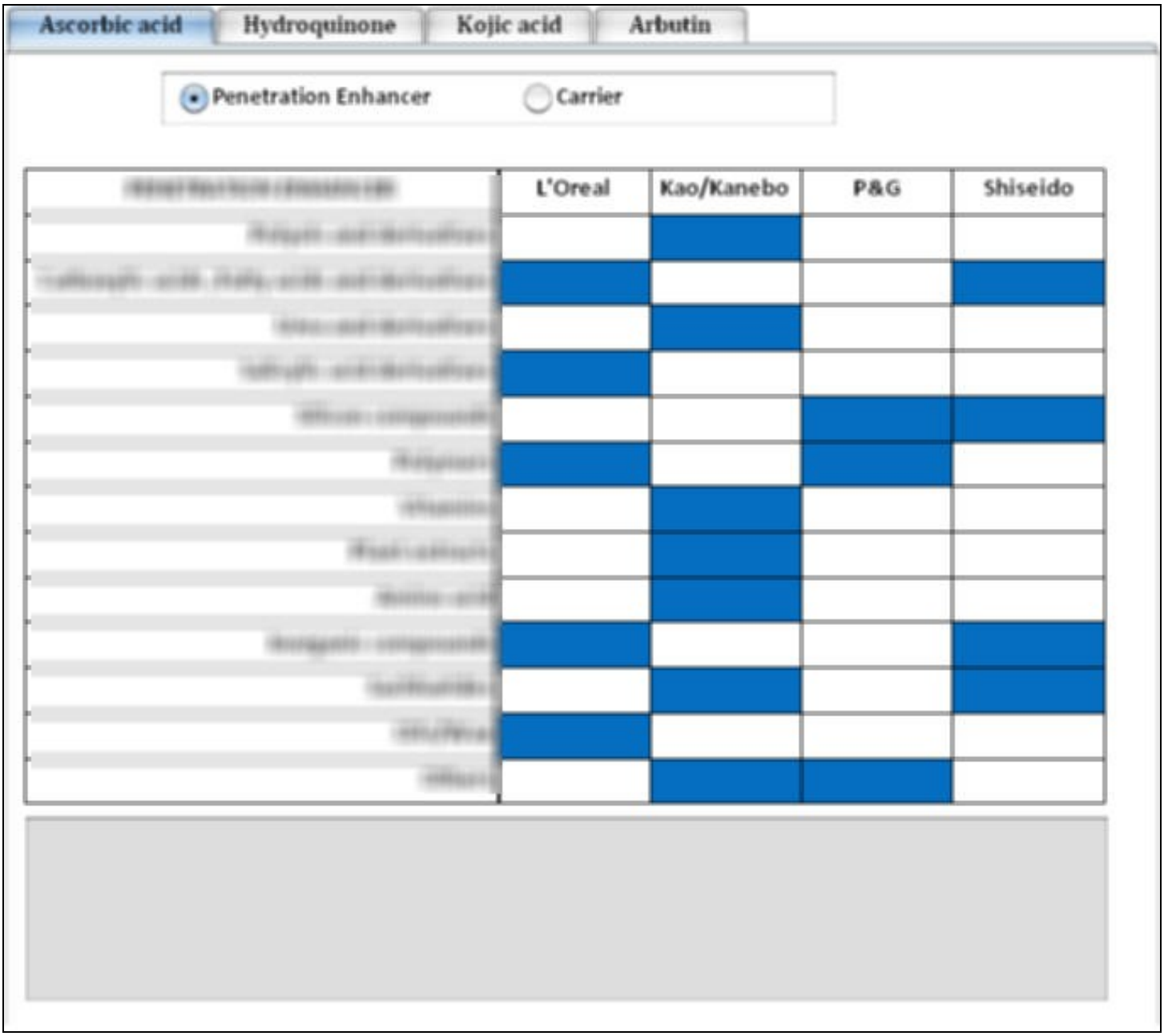
Key Points

- Vitamins and Salicylic acid derivatives are preferably dissolved in lower alcohols
- Inorganic compounds are used with a wide range of solvents like higher & lower alcohols, acids & derivatives, etc.
- Polyols are used in conjunction with solvents such as glycol, glycerol, lower alcohols and acids

Delivery strategies for whitening actives

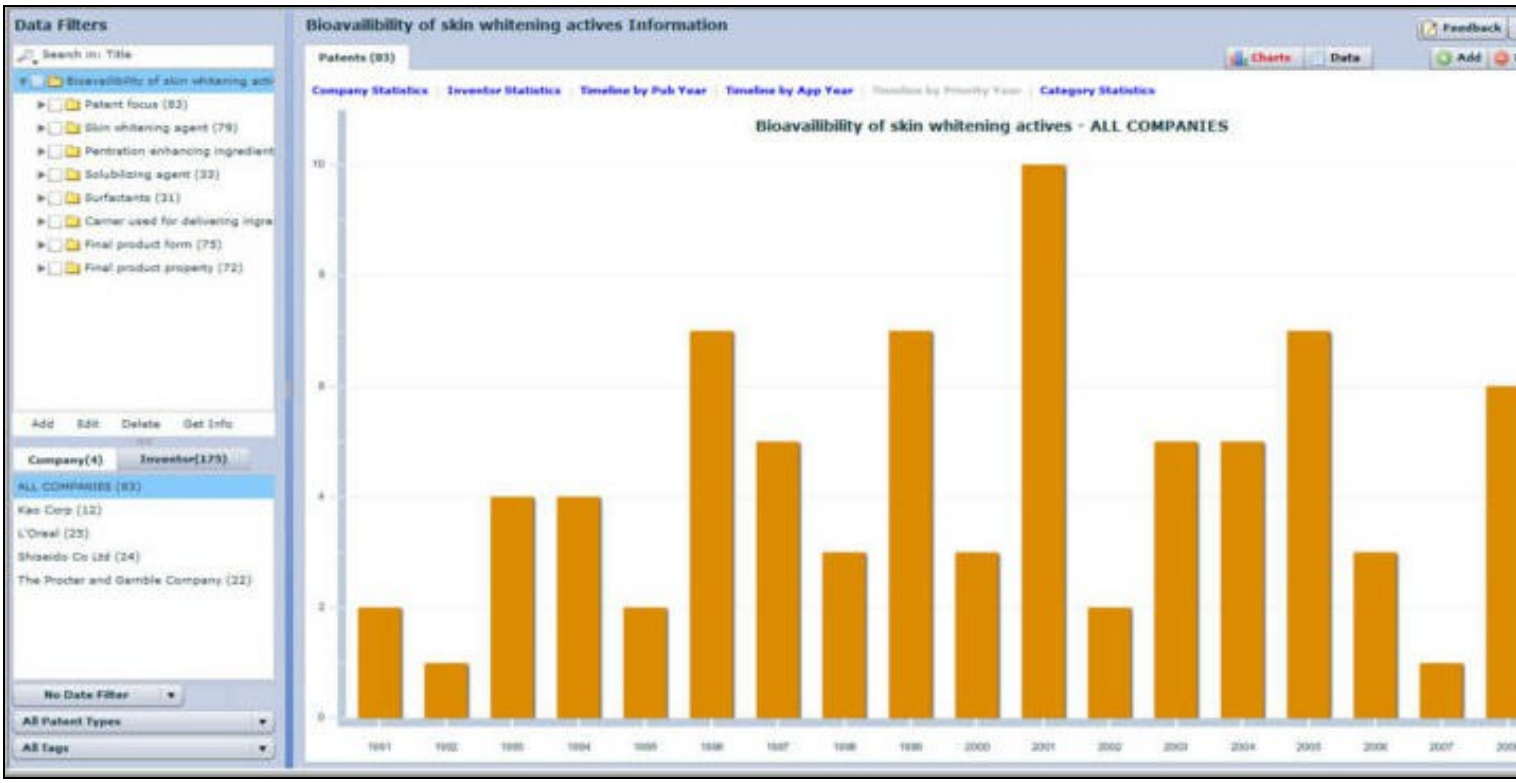
- The most common skin-whitening agents have been mapped with the usage of penetration enhancer and carrier across the assignees.

- **Click on the appropriate tab for each active.**
- **Each colored cells will give the corresponding information of delivery ingredients/methods**



Dashboard

A preview of the dashboard is shown below.


Data Filters
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Patent focus (83)
Skin whitening agent (79)
Pentration enhancing ingredient
Solubilizing agent (33)
Surfactants (31)
Carrier used for delivering ingre
Final product form (75)
Final product property (72)
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Company(4)
Inventor(175)
ALL COMPANIES (83)
Kao Corp (12)
L'Oreal (25)
Shiseido Co Ltd (24)
The Procter and Gamble Company (22)
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Bioavailibility of skin whitening actives Information
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