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Nuts and Bolts of Oil and Temperature in Topical Preparations of Salicylic Acid

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Background: Traditional formulations of salicylic acid in ointment bases have disadvantages of being greasy and irritant due to free crystals.

Aim: To explore the method for selection of oils and their ratio for topical preparation on the basis of equilibrium solubility study of salicylic acid and to evaluate temperature effect.

Materials and methods: Scanning and calibration curve of salicylic acid in methanol were developed. Among available oils, those that had no interference of absorbance of salicylic acid were short-listed for screening purpose. Selections of oils were carried out on the basis of equilibrium solubility study. Compatibility study was made by Fourier Transform Infra-Red spectroscopy analysis. Primitive study of oil mixtures was done. Selections of the ratio of oils were carried out on basis of constrained simplex-centroid design.

Results: Salicylic acid had shown linearity in the range of 15-65 µg/mL in methanol at wavelength maximum (300 nm). From the equilibrium solubility study, Parker Neem® Oil (11.81 ± 0.5 mg/g), Isopropyl Myristate (11.29 ± 0.04 mg/g), Mogra Oil (9.62 ± 0.94 mg/g) were selected. The study possessed the same main Fourier transform infra-red peaks of salicylic acid in the salicylic acid-oils physical mixture. 58.64% Parker Neem® oil and 41.36% isopropyl myristate mixture was selected as optimized batch with the desirability of 0.391.

Conclusion: The oils mixture could be selected for topical preparation of salicylic acid like paste, cream, ointment etc.

BACKGROUND

Skin covers very much high area of the body and is the largest organ of the body and contains hair follicles, sweat ducts, too. As fatty acids and sweat are secreted from sebum, pH of skin is acidic in nature. The skin has multiple layers of cells which are divided into epidermis i.e. superficial layers and dermis i.e. deeper layers. Dermis is located below the epidermis and has multiple layers and contains large numbers of different structures.¹

Secondary cutaneous infection involvement is due to any bacterial, fungal, viral or parasitic agent. Skin diseases are a significant problem all over the world. Fungal diseases in human are caused by inhalation of conidia, invasion of mucous membrane, contamination of wounds with candida or mycelia fragments, etc.² Topical fungal skin infections are dermatophytosis, ringworm, dandruff, athlete's foot, onychomycosis, candidiasis (yeast infections), aspergillosis, fusariosis. The success of fungal treatment

in invasive fungal infections depends on how early in the course of infection that treatment has been instituted. Choice of treatment is based on several factors³. There are three major categories of anti-fungal drugs currently available for targeting different cell functions: the integrity of cell membrane, ergosterol biosynthesis, and integrity cell wall.⁴

Chemically salicylic acid is 2-hydroxybenzoic acid ($C_7H_6O_3$). It has a molecular weight of 138 g/mol, melting point of 158–161°C. It is white or colorless, acicular crystals or a white, crystalline powder. It possesses the solubility of 2.48 mg/g in water and 625 mg/g in methanol. It has log p-value of 2.26. It belongs to BCS Class I. 10% w/w solution has pH of 2. Pka value is 2.97.⁵ It is derived from the bark of *Salix alba* and leaves of wintergreen. It is synthetically manufactured too. It was extracted for the first time by Buchner JA in early 19th century. It possesses antimicrobial, keratolytic, analgesics (salicylates) actions. Moreover, it could

be used for various categories such as moisturizing, skin, hair conditioner, etc.⁶ The side effects of the salicylic acid include sensitivity, excessive drying, and irritation. Topical salicylic acid preparations like *Betex Super* cream[®], *Betex* ointment[®], *Sapat malam*[®], *sapat plus malam*[®] etc. do not contain oil portion. They contain ointment base. *Betex Super* cream[®], *Betex* ointment[®], *Sapat malam*[®], *sapat plus malam*[®] etc. (Registered brands in the Indian subcontinent pharmaceutical market) are coarse in texture and microscopic examination show crystals of salicylic acid. These tests confirmed that 8–10% of salicylic acid is not completely solubilized in ointment base for keratolytic effect, so lesser penetration through stratum corneum. Traditional formulations of it in ointment bases have disadvantages of being greasy and irritant due to free crystals.⁷ It softens the scaly layers of skin and eases their removal. It is applied to palms, soles, and scalp in concentrations of 2–10%. Salicylic acid is especially useful in combination with corticosteroids to enhance penetration and improve clinical efficacy.⁸ MIC for *Candida albicans* is very poor 8.9–22.33 mg/mL.⁹

AIM

To explore the effect of oils, their ratio, and temperature for topical preparation of salicylic acid.

MATERIALS AND METHODS

MATERIALS

Salicylic acid was purchased from Sewa fine Chem. Ahmedabad, India. Parker Neem[®] oil was purchased from Parker Biotech Pvt. Ltd. Chennai, India. Mogra oil, Black till oil, coconut oil, lemon oil, clove oil, lavender oil, heavy liquid paraffin, light liquid paraffin, and benzene were purchased from Astron Chemicals Ltd, Ahmedabad, India. Isopropyl myristate, turpentine oil, eucalyptus oil, olive oil, sesame oil, peppermint oil, oleic acid, mentha oil, bitter almond oil, isopropyl palmitate, methanol, and triacetin were purchased from Chem dye Corporation, Rajkot, India. Neem oil was gift sample from Green Well Biotech, Rajkot, India.

METHODS

SCANNING AND CALIBRATION CURVE OF SALICYLIC ACID IN METHANOL

1 mg salicylic acid was taken, add methanol, carry out sonication by Sonicator (SUG-321, Remi Equipment Ltd, India) for 5 min, the volumes were made up to 100 ml with methanol in 100 mL volumetric flask (Borosil[®] Pvt. Ltd). This was a stock solution

(10 µg/mL) of salicylic acid. From it, different salicylic acid solutions were prepared in methanol, in the range of 10–25 µg/mL concentration and UV-scan was taken between wavelength ranges of 200–400 nm by the double beam UV-visible spectrometer (LT-2900, Labtronics (I) Pvt. Ltd, India). A wavelength at which solutions showed maximum absorbance was selected as absorbance maximum ($\lambda_{\max}$) in nm for further analytical work.¹⁰ The absorbance of these different solutions was measured at $\lambda_{\max}$.¹¹ The standard graph for salicylic acid was made by putting the concentration of salicylic acid (µg/mL) on X-axis and the average absorbance at $\lambda_{\max}$ on the Y-axis (Microsoft Word[®], version Professional Plus 2010, Microsoft Corporation, Redmond, USA).¹²

SHORT-LISTING, SCREENING, AND OPTIMIZATION OF RATIO OF OILS MIXTURE

Among available oils, oils that had no interference of absorbance of salicylic acid were short-listed for screening purpose. If fewer absorbance in 200–400 nm were found, then that was checked by observing the absorbance of salicylic acid at $\lambda_{\max}$ or not. Among the shortlisted oils, screening of oils was made on the basis of equilibrium solubility study. Salicylic acid was added in an excess amount in 5 mL of oil to be screened and then the mixture was stirred continuously for 1 h at 50 rpm and at ambient temperature in Orbital shaking incubator (IHB-164, Remi Equipment Ltd, India) following attainment of equilibrium. The mixtures were allowed to stand for one day at a side with occasional shaking. The mixtures were then allowed to shake for 15 min at 50 rpm and ambient temperature in the shaker bath. The obtained supernatant was filtered using filter paper of 11 µ pore size (Chem dye Corporation, Rajkot, India). Spectrophotometric measurement of the filtrate was measured at the $\lambda_{\max}$. Solubility study data were used for screening or selection of oils.¹³ A mixture of oil was taken instead of single oil, so the ratio of oils was optimized by applying constrained simplex-centroid design and optimization was done within the interior of triangle region. One checkpoint batch was also carried out for validation of design. Applying Design[®] Expert trial version 8.0.7.1 (State Ease Inc., MN, USA) optimized ratio was selected with maximum desirability and all the same parameters were also evaluated for optimized batch.^{14,15}

Density: It was determined by 10 mL capacity specific gravity bottle of Borosil[®] Pvt. Ltd.

Viscosity: It was determined by Oswald's Viscometer of Borosil[®] Pvt. Ltd.

Organoleptic tests: Color, odor, and homogeneity of oils mixture were checked by organoleptic means.

pH: pH of oils mixture with 10% w/w of salicylic acid was very low, so check by indica® (pH indicator paper, Merk specialties, Mumbai, India).¹⁶

Compatibility study: Compatibility study was carried out by FTIR (Fourier Transform Infra-Red) spectroscopy analysis. A mixture of oils and salicylic acid were mixed geometrically and analyzed by FTIR-8400 spectrophotometer, Shimadzu, Japan in the scanning range of 400–4000 cm^{-1} and resolution 1 cm^{-1} too.¹⁷

Statistical Analysis: Divide solubility data of salicylic acid in two groups. Group-I: solubility of salicylic acid at 70°C. Group-II: solubility of salicylic acid at 30°C. Calculate the variance of groups. Find the ratio of the variance of both groups. This is called F-value. Find the observed difference (SD) between means of two groups. Calculate standard error (SE) of difference between means of two groups. The ratio between SD and SE is unpaired student's *t*-test value. The significance of F-value and *t*-value were found by referring to Microsoft Excel Worksheet®, version Professional Plus 2010, Microsoft Corporation, Redmond, USA. All data were represented as mean of five independent experiments $\pm$ Standard deviation (SD). All tests were performed at 5% level of significance.¹⁸

RESULTS

Salicylic acid had wavelength maximum of 300 nm in methanol (**Fig. 1**). Salicylic acid showed linearity in the range of 15–65 $\mu\text{g/mL}$ in methanol at 300 nm wavelength maximum (**Fig. 2**). Oils were screened out that had no absorbance in between 200–400 nm (**Table 1**). From the solubility values of salicylic acid, oils presented in **Table 2**, Parker Neem® Oil (Antifungal oil), Isopropyl Myristate (Penetration enhancer oil), Mogra Oil (Solubility enhancer/ flavoring oil) were selected for the prospective study. Using constrained simplex-centroid design different batches of oil mixtures were formulated (**Table 3**) and evaluated (**Table 4**).

Salicylic acid-oils physical mixture (12th Batch) exhibits (**Fig. 3**) main FTIR peaks at 2926.01 cm^{-1} , 1373.32 cm^{-1} , 1614.42 cm^{-1} , 1456.26 cm^{-1} , 1373.32 cm^{-1} , 1230.58 cm^{-1} , 1109.07 to 1176.58 cm^{-1} , 723.31 to 758.02 cm^{-1} , 2528.68 to 2852.72 cm^{-1} . These were characteristic absorption peaks of C-H stretching (3018.60–2821.86 cm^{-1}), C=O (COO-) symmetric (1384.89 cm^{-1}), C=C (phenolic) (1612.49 cm^{-1}), C-C stretching (1444.68 cm^{-1}), O-H (phenolic) bending

(1323.17 cm^{-1}), COO- (C-O) stretching (1294.24 cm^{-1}), C-OH (phenolic) stretching (1157.29 cm^{-1}), vibrational peaks of = C-H bending (659.66 to 698.23 cm^{-1}), R-COOH (2532.54 to 2821.86 cm^{-1})

Tabulated F-value at infinite % level of significance is 1.96. Calculated F value of salicylic acid was very much lower than tabulated at infinite %, therefore, it was insignificant and samples may very well be regarded as drawn from the same population, i.e. homogeneity of variances and *z*-test or *t*-test was carried out. Two independent samples of solubility at 30°C and 70°C with sample size were thirty so Student's unpaired *t*-test was carried out. Pooled degree of freedom (15+15-2) 28, tabulated *t* value at 5% level of significance is 2.05. Calculated *t* value was higher than tabulated, *p* less than 0.05. It can occur less than 5 times in 100 i.e. rarely by chance. The difference was real in 95% experiments, hence highly significant (*t* = 2.67, *p* less than 0.05 or significant at 0.05%).

Batch 12 was selected with the maximum desirability of 0.391 and was considered for topical preparation. Formulation and evaluation of the 12th batch were carried out for validation and % bias found to be satisfactory for the purpose of topical preparation.

DISCUSSION

Topical salicylic acid preparations like *Betex Super cream*®, *Betex ointment*®, *Sapat malam*®, *sapat plus malam*® etc. do not contain oil portion. The base of formulations is white soft paraffin. This would not solubilize salicylic acid, therefore, lesser penetration through stratum corneum. Till date no any formulation is available in the market in which 10% w/w salicylic acid is solubilized in formulation with the influence of temperature and/or utilization of optimized ratio of oil mixture for the method of preparation. The study for the first time provides technology to solubilize high amount of 10% w/w salicylic acid in the keratolytic formulation by means of the use of oils mixture and temperature. Oils also had their own properties like antifungal, penetration enhancer, etc. too.¹⁸ FTIR study has confirmed that salicylic acid is compatible with oil mixture.^{19,20} If salicylic acid is available as solubilized form, it will provide good penetration property, bioavailability followed by a better keratolytic effect.⁷ Solubility at 30°C and at 70°C was the highest for the optimized (the 12th) batch. Statistical analysis has proved that all samples had the high solubility of salicylic acid at 70°C than that of 30°C.

Table 1. Short-listing of oils for equilibrium solubility study of salicylic acid

Oil	Reason for selection/ rejection	Inference
Neem oil	No absorbance between 200–400 nm and strong antifungal	No
Parker neem® oil	No absorbance between 200–400 nm and strong antifungal, antibacterial	Yes
Black till oil	No absorbance between 200–400 nm and antifungal	No
Coconut oil	No absorbance between 200–400 nm and antifungal	Yes
Lemon oil	No absorbance at 200–400 nm and antifungal	No; skin irritant
Clove oil	No absorbance at 200–400 nm and penetration enhancer	No; skin irritant
Lavender oil	No absorbance between 200–400 nm and antifungal	Yes
Heavy liquid paraffin oil	No absorbance between 200–400 nm and pharmaceutically inert; also used in every Emulgel	Yes
Light liquid paraffin oil	No absorbance between 200–400 nm and pharmaceutically inert also used in every Emulgel	Yes
Turpentine oil	absorbance between 200–400 nm, skin irritant	No
Eucalyptus oil	absorbance between 200–400 nm, skin irritant	No
Olive oil	No absorbance at 200–400 nm and penetration enhancer	Yes
Sesame oil	No absorbance between 200–400 nm and antifungal	No
Isopropyl myristate	No absorbance between 200–400 nm and penetration enhancer	Yes
Peppermint oil	No absorbance at 200–400 nm, antifungal, antibacterial and penetration enhancer	Yes
Oleic acid	No absorbance at 200–400 nm and penetration enhancer	Yes
Mogra oil	No absorbance at 200–400 nm, antifungal, antibacterial, fragrance and penetration enhancer	Yes
Mentha oil	No absorbance at 200–400 nm, antifungal, antibacterial and fragrance	Yes
Bitter almond oil	No absorbance between 200–390 nm, antibacterial and antifungal	Yes
Isopropyl palmitate	No absorbance at 200–400 nm and penetration enhancer	Yes
Triacetin	No absorbance between at 200–400 nm and penetration enhancer	Yes

Yes: selected for equilibrium solubility study;
 No: Not selected for equilibrium solubility study.

Table 2. Equilibrium solubility study of salicylic acid in selected oils

Category	Type of oil	Solubility (mg/g) at 30°C temperature
1	Parker neem® oil	11.81 ± 0.5
	Coconut oil	9.80 ± 0.63
	Lavender oil	10.71 ± 0.07
	Heavy liquid paraffin oil	2.48 ± 0.03
	Light liquid paraffin oil	2.50 ± 0.07
	Olive oil	9.66 ± 0.03
2	Isopropyl myristate	11.29 ± 0.04
	Peppermint oil	11.11 ± 0.81
	Oleic acid	8.79 ± 0.81
	Triacetin	7.01 ± 0.01
	Isopropyl palmitate	9.97 ± 0.15
	Mogra oil	9.62 ± 0.94
3	Mentha oil	9.54 ± 0.11
	Bitter almond oil	9.01 ± 0.39

Mean ± SD; n=5; one oil from each category oil was selected. Category: 1: Antifungal oil, 2: Penetration enhancer oil, 3: Solubility enhancer / flavoring oil.

Table 3. Formulation of different batches of oil mixtures with salicylic acid

Batch	Code value			Decoded value (%)			
	Parker Neem® oil	Isopropyl Myristate	Mogra oil	Parker Neem® oil	Isopropyl Myristate	Mogra oil	Salicylic acid
1	1	0	0	70	20	0	10
2	0	1	0	50	40	0	10
3	0	0	1	50	20	20	10
4	0.5	0.5	0	60	30	0	10
5	0.5	0	0.5	60	20	10	10
6	0	0.5	0.5	50	30	10	10
7	1/3	1/3	1/3	56.67	26.67	6.67	10
8	2/3	1/6	1/6	63.4	23.4	3.4	10
9	1/6	2/3	1/6	53.4	33.4	3.4	10
10	1/6	1/6	2/3	53.4	23.4	13.4	10
11*	0.5	0.25	0.25	60	25	5	10
12	0.139	0.861	0	58.64	41.36	0	10

*Checkpoint batch.

Table 4. Evaluation of different batches of oil mixtures

Batch	Solubility (mg/g)		Density (g/ml)	Viscosity (cP)	pH	colour	odor	Homo-geneity
	At 30°C temp	At 70°C temp						
1	10.49±0.36	11.23±0.86	0.995±0.001	20±1	2.2±0.45	Yellow	Specific bitter	Good
2	10.35±0.27	52.23±0.57	1.012±0.002	25±2	2.2±0.45	Yellow	Specific bitter	Good
3	10.05±0.45	14.89±0.02	0.986±0.001	27±1	2.2±0.45	Yellow	Specific bitter	Good
4	10.42±0.31	10.91±0.18	1.003±0.002	28±1	2.2±0.45	Yellow	Specific bitter	Good
5	10.27±0.40	11.72±0.11	0.990±0.001	33±2	2.2±0.45	Yellow	Specific bitter	Good
6	10.2±0.36	12.17±21.45	0.999±0.001	34±3	2.2±0.45	Yellow	Specific bitter	Good
7	10.3±0.36	15.41± .09	0.998±0.002	35±4	2.2±0.45	Yellow	Specific bitter	Good
8	10.39±0.36	22.93±0.15	0.996±0.002	22±1	2.2±0.45	Yellow	Specific bitter	Good
9	10.32±0.31	13.25±0.13	1.005±0.002	29±1	2.2±0.45	Yellow	Specific bitter	Good
10	10.17±0.4	13.46±0.45	0.992±0.001	18±1	2.2±0.45	Yellow	Specific bitter	Good
11*	10.34±0.36	10.6±0.07	0.997±0.001	23±1	2.2±0.45	Yellow	Specific bitter	Good
Water	2.47±0.01	13.64±0.53	1.000±0.001	1±0.1	7±0.01	No	No	Good
	10.59 ± 0.5	15.1±0.17	0.977±0.001	88±5	6±0.02	Yellow	Specific bitter	Good
12	10.45±1.71	19.75±0.07	1.002±0.002	18± 1	2.2±0.45	Yellow	Specific bitter	Good
Benzene	9.98±0.01	50±0.02	n/d**	n/d**	n/d**	n/d**	Aromatic	Good

*Checkpoint batch; n=5; Mean ± SD; n/d** not derived.

Figure 1. Scanning of salicylic acid in methanol; Y-axis is denoted absorbance and X-axis is denoted wavelength (nm). The first, second, third, and fourth curves from upward to downward had a concentration of 35 µg/mL, 30 µg/mL, 25 µg/mL, and 20 µg/mL concentration of salicylic acid in methanol and showed absorbance of 0.438, 0.356, 0.337, and 0.292 respectively at 300 nm.

CONCLUSION

Selected oil combinations (Batch 12) for salicylic acid had the highest solubility of salicylic acid at 30°C and 70°C temperature too. Elevation of temperature to solubilize salicylic acid is more effective technology. This oils ratio (Batch 12) could be selected for topical preparation of salicylic acid like cream, ointment etc. This leads to solving the problem of solubility of salicylic acid. Oil portion provides more penetration through stratum corneum as compared to hydrophilic phase. It acts as the chemical penetration enhancer and temporarily breakdown lipid-protein and protein-protein bond of skin structure.

LIMITATIONS

The study was limited to less number of oils used for short listing and screening purpose.

CONFLICT OF INTEREST

All authors declare that they have neither conflict of interest nor funding source.

AUTHORS' CONTRIBUTIONS

The concept, research design, literature review,

Figure 2. Calibration curve of salicylic acid in methanol at 300 nm. Mean $\pm$ SD; $n=5$. $y = 0.012x + 0.0165$; $R^2 = 0.9955$.

Figure 3. FTIR spectra of salicylic acid and physical mixture of excipients of 12th Batch; green line indicates salicylic acid and red line indicates 12th Batch.

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AUTHORS' DISCLOSURES

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DISCLAIMER

Any opinion, findings, and conclusions or recommendations expressed in this material are those of the corresponding author only.

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Основные положения практического применения масел и температуры в препаратах местного действия с содержанием салициловой кислоты

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Введение: Традиционные препараты салициловой кислоты в мазевых основах отличаются тем недостатком, что они жирны и вызывают раздражение за счёт свободных кристаллов в них.

Цель: Исследовать метод селекции масел и их соотношения для препаратов местного действия на основе исследования равновесной растворимости салициловой кислоты и осуществить оценку температурного эффекта.

Материалы и методы: Были проведены сканирование и построена калибровочная кривая салициловой кислоты в метаноле. Среди наличных масел, не имеющих интерференции абсорбции салициловой кислоты, были подобраны подходящие для целей проведения скрининга. Подбор масел был осуществлён на основе исследования равновесной растворимости. Исследование совместимости было осуществлено при помощи анализа с применением инфракрасной спектроскопии с преобразованием Фурье. Были осуществлены основные исследования масляных эмульсий. Подбор соотношения масел был осуществлён на основе ограниченного симплекс-центроидного плана (constrained simplex-centroid design).

Результат: Салициловая кислота показала линейность в диапазоне 15-65 $\mu\text{g}/\text{мл}$ в метаноле при максимальной длине волны (300 nm). После исследования равновесной растворимости были выбраны масло Parker Neem® (11.81 ± 0.5 мг/гр), Изопропил Миристат (11.29 ± 0.04 мг/гр) и масло арабского жасмина (9.62 ± 0.94 мг/гр). Исследование установило те же самые основные пики инфракрасного преобразования Фурье салициловой кислоты и в эмульсии салициловой кислоты и масел. Была выбрана эмульсия 58.64 % масла Parker Neem® и 41.36% Изопропил Миристат в качестве оптимизированной партии с целесообразностью 0.391.

Заключение: Эмульсия из масел может быть выбрана в качестве препарата местного действия с салициловой кислотой в виде пасты, крема, мази и т.д