Compounded drugs and formulations in dermatology

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Introduction

Compounding topical formulations is an old art in dermatology. The United States (US) Food and Drug Administration (FDA) defines compounding as a process of combining, mixing or altering ingredients of a drug by a licensed pharmacist or under his supervision or a licensed physician to make a medication tailored to the needs of individual patients.[1] In the US, compounded drugs constitute 1%–3% of the prescriptions. Many topical prescriptions are still dispensed as compounded formulations. In India, registered medical practitioners can legally dispense medications for their patients and can get drugs compounded through pharmacies for their patients. State law may permit registered practitioners to compound medications in the office/clinic for a patient's immediate needs.[2]

Despite advancements in stabilising the active drug in topical formulations and ensuring maximum drug delivery, some special clinical situations may still demand compounding of certain formulations. There can be serious adverse effects or contraindications with systemic formulations that can make patients desire compounded topical formulations over the systemic ones. The desired topical formulations are usually commercially unavailable, especially if they have recent or rare indications which are financially not feasible for pharmaceutical companies to manufacture. Children need oral solutions rather than tablets or capsules, but often solutions of many medications are not available, and need compounding.

These topical agents are often prepared by mixing the powdered tablet in a petrolatum base to form ointments or injection forms in an aqueous or alcoholic base to form solutions. Compounding pharmacies and dispensaries or pharmacology departments of various institutes can help make these preparations.

This article summarises various ways dermatologists use to compound these preparations, along with their efficacy in different diseases.

Topical formulations

Sodium thiosulphate and sodium metabisulfite

Treating calcinosis cutis presents challenges, especially when it occurs alongside connective tissue diseases such as systemic sclerosis or juvenile dermatomyositis. Compounds like sodium metabisulfite and sodium thiosulphate are utilised for this purpose. They chelate calcium and enhance its solubility in the bloodstream, leading to the formation of more soluble calcium salts. Initially employed intravenously for calciphylaxis with promising results, sodium thiosulphate has also been explored in topical and intralesional forms for calcinosis cutis secondary to various causes, thereby mitigating potential side effects linked with intravenous administration. These compounds are obtainable in crystal form from various sources including online suppliers. The crystals can be pulverised into a powder either manually or in a pestle and mortar. Concentrations between 10% and 25%, compounded with petrolatum or cream base, have been utilised.[3] In solution form, sodium thiosulphate but not metabisulfite, has been administered intralesionally weekly to monthly at concentrations ranging from 40 to 250 mg/dL, typically in doses of 0.1 mL/cm^2 to the lesion base, over 3–6 months. This approach has shown positive outcomes, particularly in reducing the size of calcinosis cutis nodules.

In a systematic review, out of 48 cases treated with topical sodium thiosulphate, 39 (81%) cases showed clinical improvement and nine (19%) showed complete response after a median of 3.9 months.[4] With intralesional sodium thiosulphate, out of 53 cases treated, 39 (74%) showed clinical

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improvement and 19 (36%) showed complete response after a median treatment duration of 1 month.[4]

Phenytoin

Phenytoin, when compounded in a topical formulation with petrolatum or zinc oxide, has been shown to heal cutaneous and mucosal ulcers faster than controls, including trophic ulcers due to leprosy.[5,6] Its systemic side effect of gingival hyperplasia instigated studies to show its effect on the formation of granulation tissue and hastening healing.

Both phenytoin paste and suspension have been successfully used to treat non-healing ulcers. For preparation of phenytoin paste, 10 commercially available tablets, each containing 100 mg of phenytoin sodium, are crushed manually or with pestle and mortar and mixed with 100 g of zinc oxide paste or petrolatum ointment/jelly yielding 1% phenytoin formulation. The formulation can also be made using 100 mg of pure phenytoin sodium powder obtained from pharmacological companies.

In a study, 70% of trophic ulcers of leprosy showed complete healing by 12 weeks using phenytoin paste compared to none in the control group who used 2% zinc oxide paste.[5] Similarly, 100–200 mg of pure phenytoin sodium powder, obtained from pharmacological companies, is dissolved in 5 mL of normal saline (0.9% NaCl) solution forming 2%–4% phenytoin-NaCl suspension. This formulation can be applied once or twice daily over the trophic ulcers of leprosy, followed by occlusion with gauze. Healing takes a few days to weeks depending upon the size of the ulcer. In a study, 2%–4% phenytoin suspension led to the complete healing of 73.4% of ulcers by 4 weeks, compared to none in normal saline controls.[6]

Sirolimus

Topical sirolimus shows promising results in treating angiofibromas associated with tuberous sclerosis, especially in children, who do not tolerate ablative procedures under local anaesthesia. However, it is commercially unavailable in India. Tablet sirolimus is available as 1 mg or 2 mg and comes in packs of six tablets. Ten tablets of 1 mg each are crushed and mixed with 10 g of petrolatum ointment/jelly to prepare 0.1% ointment. In a split-face study, 0.1% sirolimus ointment prepared manually and applied twice daily, led to a significant reduction in facial angiofibroma severity index over 3 months over the facial half where it was applied, with no change on the control side.[7]

Portwine stains (PWS) have also been treated with dual therapy of pulsed dye laser (PDL) and 0.2–1% sirolimus ointment, with conflicting results. In a series of five cases showing modest response with pulsed dye laser alone, a significant improvement over a short duration was demonstrated by adding 0.5–1% topical sirolimus.[8] In another series of 15 PWS cases, the addition of 0.2% sirolimus ointment to pulsed dye laser for 4 months led to significant subjective improvement (based on investigator and patient global assessment scores) but did not improve PWS erythema using calorimetric assessment. Sirolimus led to itching and dryness (86.7% of cases) and contact dermatitis (20% of patients) in these cases.[9]

Higher concentrations of 1%–2% are 10 times more expensive to formulate, and solution formulations cause more irritation. Although the effect size is not huge, and stoppage leads to recurrence, topical sirolimus can be used in children who are not willing/suitable for ablative procedures, and as maintenance therapy after procedures.

Tranexamic acid (TA)

Oral tranexamic acid is effective in treating melasma. Although topical tranexamic acid, 2–5%, might be less effective than oral therapy, it is free from systemic side effects. Both patients and doctors are more comfortable continuing it for a longer duration, which is especially desirable in a disease like melasma that frequently recurs and requires maintenance treatment. It can also be combined with other topical depigmenting agents with different mechanisms of action, leading to a potential synergistic effect.

A split-face study showed 3% tranexamic acid, applied twice daily, to be as effective as a combination of 3% hydroquinone with 0.01% dexamethasone after 12 weeks of treatment.[10] Although topical tranexamic acid is now commercially available in various formulations like creams, gels, and sera alone or in combination, it is still being compounded at places where topical formulations are not easily available. Six tablets of tranexamic acid, 500 mg each, comprising 3 g total, are dissolved in 10 mL of 96% ethanol plus 10 mL of 1,3-butanediol with distilled water added up to 100 mL; to make a 3% concentration.[10] Alternatively, injectable formulations can also be used. Injectable tranexamic acid is available at a concentration of 100 mg/mL (=10%), which can be diluted by half to 5% by adding equal parts of sterile water.[11] Local side effects include itching, burning and erythema, but their frequency is less when compared to 3% hydroquinone.[11]

Metformin

Metformin is commonly used as an oral hypoglycaemic drug. Recently, the melanogenic action of topical metformin has been demonstrated in an in vitro study, and hence, tried as a treatment option for melasma.[10,11] It has similar advantages as topical TA, including safe usage for long-term maintenance. It can be compounded as a lotion in a 30% weight-to-volume ratio by mixing 30 g of metformin powder (sourced from pharmaceutical companies) with 70% alcohol and propylene glycol. The prepared 30% metformin lotion is stored in amber-coloured glass bottles.

In a randomised controlled trial using such a preparation, improvement in melasma was reported in 13 out of 20 (65%) patients without any serious adverse effects after 8 weeks of

use, which was comparable to the triple combination cream used in the control group.[12]

In another formulation, 30% cream was compounded by crushing and mixing 60 commercially available tablets, each containing 500 mg metformin, in a similar 70% alcohol and propylene glycol base. With this preparation also, a study reported comparable improvement in melasma as with triple combination therapy after 8 weeks.[13]

The above discussed topical formulations have been summarised in Table 1.

Miscellaneous preparations

Apart from the above-mentioned drugs, many other formulations are not commonly compounded nowadays. Either they are infrequently used due to the availability of better alternatives, or their topical formulations are readily available commercially, or compounding them is cumbersome. They include:

i) Whitfield ointment – for 5 g Whitfield ointment, an emulsifying wax is prepared by melting 1.23 g of cetostearyl alcohol in a porcelain dish over a water bath, and 0.135 g of sodium lauryl sulphate is added and mixed. 0.5 mL of water is further added, and the mixture is heated well (around 60°C) till frothing ceases. This 1.365 g emulsifying wax is mixed well with 2.275 g white soft paraffin and 0.910 g liquid paraffin to form the emulsifying ointment. 150 mg of salicylic acid and mg of benzoic acid are triturated into fine powders in a mortar and then levigated by slowly adding the melted emulsifying ointment to create the final Whitfield ointment. Alternatively, a readily available polyethylene glycol ointment can be used as a base.

ii) Coal tar ointment – a variety of methods and formulations exist. For one such formulation, 1–10% coal tar ointment can be prepared by mixing 20% coal tar solution obtained from pharmacies with an emulsifying ointment containing emulsifying wax, white soft paraffin and liquid paraffin. Salicylic acid

Table 1: Compounded topical formulations in dermatology

S. No.	Drug	Conc.	Indication	Results
1	Sodium thiosulphate and sodium metabisulfite	10%–25%, prepared from crystals obtained from chemists	Calcinosis cutis	39/48 (81%) had some clinical improvement, out of which 9/48 (19%) showed complete response after a median of 3.9 months[4]
2	Phenytoin paste	1% paste, prepared from tablets crushed and mixed in zinc oxide paste	Non-healing ulcers including neuropathic ulcers of leprosy and mucosal ulcers	30/43 (70%) leprosy patients with trophic ulcers showed complete healing by 12 weeks using phenytoin paste compared to none in the control group[5]
		4% suspension, using pure powder supplied by pharmaceutical companies, dissolved in NaCl solution		2%–4% phenytoin suspension led to complete healing of 73.4% of ulcers by 4 weeks, compared to none in normal saline controls[6]
3	Sirolimus	0.1% cream, prepared from tablets crushed and mixed with petrolatum	Facial angiofibromas	In a split-faced study of 12 patients, there was a significant reduction in the size of facial angiogfibromas over the applied size, compared to the control side[7]
		0.5%–1% cream (supplied by a pharmaceutical company)	Portwine stain	Significant improvement in a short duration after adding topical sirolimus in five cases who had only modest improvement with pulsed dye laser alone[8]
		0.2% sirolimus ointment		The addition of sirolimus ointment to pulsed dye laser for 4 months led to significant subjective improvement (based on investigator and patient global assessment scores) but did not improve erythema using calorimetric assessment[9]
4	Tranexamic acid	3% solution prepared by dissolving 3 g of tranexamic acid tablets in 10 mL of 96% ethanol plus 10 mL of 1,3-butanediol with distilled water added up to 100 mL, to make a 3% concentration	Melasma	All 50 (100%) patients showed some improvement, which was as effective as a combination of 3% hydroquinone + 0.01% dexamethasone, after 12 weeks of treatment[10]
		5% solution prepared by diluting tranexamic acid injection (10%) with sterile water	Melasma	All patients (50) showed improvement comparable with 3% hydroquinone cream after 12 weeks[11]
5	Metformin	30% lotion, made by mixing 30 g of metformin powder with 70% alcohol and propylene glycol	Melasma	13/20 (65%) patients showed improvement after 8 weeks as effective as triple combination therapy[12]
		30% cream, prepared by crushing and mixing 60 tablets of metformin (500 mg) with 70% alcohol and propylene glycol in 30% weight: volume ratio		Comparable improvement in melasma with triple combination therapy after 8 weeks in 20 patients in each group[13]

can be added at a desired concentration. For coal tar solutions, 20% solution can be diluted with a solvent like isopropyl alcohol or propylene glycol.

iii) Urea - although 40% urea cream is available now, at places where it is not available, 40% urea, 5% white beeswax (or paraffin), 20% anhydrous lanolin, 25% white petrolatum and 10% silica gel type H can be compounded through a pharmacy for chemical avulsion of dystrophic nails.

iv) Monobenzyl ether of hydroquinone – although a cream with a 20% concentration is commercially available in India, higher concentrations can be compounded through pharmacies.

Oral liquid formulations

Propranolol

Propranolol is the drug of choice for infantile hemangiomas.[14] However, propranolol in solution form is commercially unavailable and oral formulations are unsuitable for young children. Propranolol solution can be prepared by crushing or directly dissolving a 10 mg tablet of propranolol in 10 mL sterile water forming 1 mg/mL concentration, which can be put in a 10 mL syringe. A 1–3 mg/kg dose can be readily dispensed, and can be easily administered by the parents. Dose escalation can also be easily undertaken. This solution may be consumed within 2 weeks of preparation when stored in a refrigerator. The solution can also be mixed with milk or juices for palatability.

Naltrexone

Low-dose naltrexone ranging from 3 to 15 mg per day is used off-label for various skin conditions which do not otherwise have an effective and consistent therapy, like Hailey-Hailey disease and prurigo.[15,16] Naltrexon is often commercially available as a 50 mg tablets and expensive. Similarly like preparing propranolol solution, the tablet can be crushed and dissolved in 50 mL of potable water (1 mg/mL solution) and measured with a 50 mL syringe. An adequate dose can be dispensed via this syringe. The safety is maintained for up to 2 weeks when refrigerated.

Acitretin

Oral acitretin has been an effective therapy for severe congenital ichthyosis and keratinising disorders in children.[17] Acitretin is commercially available in 10 and 25 mg capsules. For neonates and infants requiring less than 10 mg dose, it can be administered by opening the capsule and mixing the oily solution with honey, milk, or infant formula in appropriate concentrations. Another option is to freeze and cut the capsules to enable the administration of a 5 mg dose by halving a 10 mg capsule.

Saturated solution of potassium iodide (SSKI)

Saturated solution of potassium iodide is used for a variety of dermatoses, including infectious diseases like fixed cutaneous and lymphocutaneous forms of sporotrichosis, and inflammatory diseases like neutrophilic dermatoses and panniculitides etc., owing to its anti-neutrophilic and anti-inflammatory properties. To prepare a saturated solution, KI powder, obtained from crushing KI crystals, is added to water in small increments like 5 g, and stirred rapidly until the solute KI stops dissolving. Since the solubility of KI in distilled water is 1.42–1.46 g/mL at room temperature, it is easier to use 142-146 g of KI in 100 mL in 100 mL water directly. Rate of dissolution can be increased by heating the solution. Using a truly saturated solution, a standard dropper of volume 0.05 mL/drop contains 0.07 g of KI. Commonly a concentration of 100% weight by volume, i.e. 100 g of KI in 100 mL distilled water, is referred to erroneously as saturated solution of potassium iodide, despite it not being completely saturated. A regular drop of this concentration measures 0.05 mL and contains 0.05 mg of KI. Twenty drops given thrice daily comprise 4 g/day if 0.05 g/mL concentrated solution is used, and approxiamtely 4 g/ day if 0.07 g/mL.[18] SSKI should be stored in light-resistant containers at a temperature of 15°C –30°C.

For sporotrichosis, the frequency is thrice daily, with an initial dosage of five drops per dose, gradually increasing by one drop/dosage, till 40–50 drops/dosage (which amounts to 2-2.5 g/dose, which when given thrice a day amounts to 6-7.5 g/day of maximum dosage), for 6–10 weeks. Common side effects of KI include stomach upset, diarrhoea, nausea, vomiting, stomach pain, lacrimation, rhinorrhoea, and iodism, which includes burning in the mouth or throat, severe headache, metallic taste and soreness of teeth and gums.

Conclusion

Dermatologists should be well-versed in the art of compounding drugs as topical formulations and oral solutions. Although the evidence could have been more robust for most of them, they have worked well in some patients. Most of them do not require buying the active pharmaceutical ingredient from pharmacological companies and they can be formulated using commercially available tablets and injections, despite their excipients. The compounding of these preparations offers us insights into developing similar formulations for newer drugs in the future.

Declaration of patient consent

Patients consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the

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