



# Formulation and Evaluation of Transdermal Patches for Migraine Treatment

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**ABSTRACT:** *Migraine is well known disease that is still under low condition of diagnosis and treatment. Most of the individuals does not get to know about the difference in normal headache and migraine outbreak. For this they usually take normal painkiller to treat migraine. Migraine attack is attached with numerous other dysfunctions like nausea, vomiting and various digestive disorders. Most of the medicines used till now are showing bitter taste which will leads to vomiting. To overcome all the challenges associated with the migraine outbreak transdermal patches are introduced to deliver drug on target. For this a suitable transdermal patch is formed to delivery drugs for all types of migraine attacks on the basis of drug concentration according to severity of the attack. According to name transdermal, it will deliver the drugs through the skin in a controlled and from the specific fixed path. The objective of our study is to find all possible combination and use of transdermal patches for the treatment of migraine. Various combinations of polymeric and plasticizer combinations ratios are being used to form transdermal patches which show effective result for migraine attack. The patches were formulated on the basis of solvent moulding method with its solvent and plasticizer as ethanol and propylene glycol respectively. For an effective treatment by transdermal patches, we need that constituents which cannot cause skin irritation or dysfunction in the migraineurs. It can also be used to release hormones in PCOD (polycystic ovarian syndrome disease) and also can help to reduce labour pain.*

**KEYWORDS:** *Absorption, Disorder, Drug Delivery, Migraine, Migraineurs, Transdermal Patches, Treatment.*

## INTRODUCTION

Numerous global studies by means of International Headache Society analytical standards have displayed that migraine is a well-known but not that much frequently diagnosed neurological situation which affect approx. 6% of male and 15%-18% of female from the general population [1]. Migraine is examined as 3<sup>rd</sup> most predominant condition globally and seventh utmost common devastating disorder [2]. Unluckily our knowledge of the pathophysiology of this disorder is deficient [3]. 90% of migraineurs approved with the proclamations that migraine is a most severe disorder than maximum persons realizes and the same peoples does not have an understanding of the difference between migraine disorder and headache. Migraine patients were also enquired to converse their approaches towards migraine disease, which exposed that patient's sense that their situation is not understood properly. The frequency of suicide in migraineurs has been seem to be greater than in the common population [4].

A Migraine is mainly a headache disease comprising of temperate to high greatness of headache related with some mixture of acute infirmity and neuro-autonomic disease like graphic or other varieties of complexion, digestive balance, deprived absorption after the minor bowel, sickness, vomiting, dizziness that get worse with locomotion, photophobia, and Sinophobia. The utmost normally mentioned purpose for not looking for cure was that it's a normal headache, while few migraineurs show that they felt that medical practioners would not be able to treat them properly, or have a very unsatisfactory visit with the same.

A lot of them does not have understanding of the migraine about the negative impact on them, how they treat their migraine attack and also when they get treated in all possible situations [5]. It is very common neurological disease, and its pathological centre and severe treatment has not been determined till now. In the current works, there is no medication that can stop an severe experience of migraine attack [6]. Gastrointestinal appearances of migraine disorder like sickness, vomiting, and gastro stasis, can reduce operative controlling of migraine problems. In general, nausea happens exactly completely at single phase or another in migraineurs in a migraine outbreak [7]. Hence, medicine distribution methods that depend on digestive motility and abdominal absorption, like drug delivery through oral, might show deliberate, unsuccessful or contradictorily operational in few patients of migraine. Delivery through injection and through nose for migraine patients is present and can surpass gastrointestinal absorption [3]. On the other hand, these methodologies might be linked with restrictive opposing actions for few patients of migraine. Few nasal spray distribution methods for migraine disease are simply used and can perform most frequently than medicine, but can be related with some bad flavour which will leads to nausea and vomiting in migraine patients.

Traditional method of treatment which need multiple dosage are not without challenges. The novel method of medicine distribution is to distribute medicine into step-wise movement at a deliberated rate, identified as monitored discharge drug delivery method [8]. Conventionally, migraine management is separated into indicative method (to let go headache pain) and defensive method (to decrease period, strength and rate of attack) [9]. Transdermal patch is an inventive medicine distribution method and can be utilizes for attaining effective systemic influence by transiting hepatic first clearance breakdown and increasing the portion absorbed. The transdermal medicinal method offered for nonstop drug discharge through whole skin into the general blood stream throughout a extend time at an existing rate.

#### *1. Benefits and drawbacks of dermal/transdermal distribution:*

Approximating numerous alternate ways of distribution, the skin equally has application and restrictions when linked with extra traditional approaches like oral medicine distribution. Overwhelming the obstacle over the previous 25 ages many studies have been accomplished to overwhelm nearly all the problems related with skin delivery method. The development of technologies built on these studies, till now has been comparatively slow. Though, the methods that have arisen over the ages can be distributed into active and passive approaches:

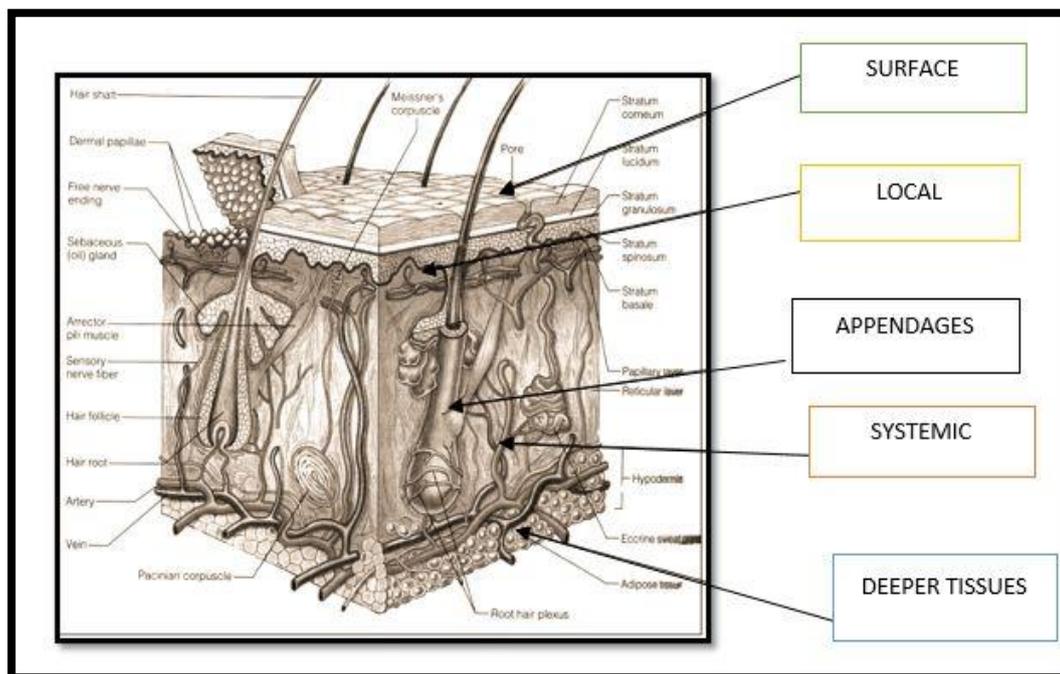
##### *1.1 Passive process:*

The traditional means of putting on of medicines to skin comprises of means of transportation like creams, ointments, passive patch and gel methodology. Further in recent times, such dose types have been established and/or reformed to improve the driving force for medicine dispersal and/or rise the porosity of the skin.

##### *1.2 Active process:*

The beginning of biotechnology in the last half of the twentieth century has directed to the development of clinically-active, great molecular weight with polar and water loving particles that are typically proteins and peptides. This type of constituents has a tendency to be comprehensively tainted by enzymes in the digestive tract if consumed through oral delivery; therefore, there is a necessity for another ways of consumption and appropriate drug distribution system. From the above Figure 1, Surface part will act as a barrier/repellent against microbes and is the site of action of sun scream and antiseptic then local part will work as a site for corticosteroids, antiviral, antihistamine, anaesthetics, and antipsoriatics. While appendages part will act as antimicrobials and depilatories, systemic area will work for hormones release, anti-hypertensive, anti-coagulants

anti-depressant etc. and deeper tissues will act for working of non-steroidal inflammatory agents [10].



**Figure 1: Anatomical and Physiological View of Skin [10]**

This is suggested that distribution of drug from other way other than oral intake would illustrates enhanced effect for the migraineurs. Moreover, fresh findings recommend that migraine patients are experiencing basic gastric immobility in the course of and in the middle of migraine outbreaks, which might affect the intestinal passage time and constitute successive minor faecal absorption of the treatment. These consequences highlight the existing truth that numerous migraine patients have less beliefs of cure benefit. Therefore, sustained development of patient training courses at the worldwide level is mandatory to increase understanding of operational migraine treatments. Furthermore, one need not to undervalue the part of the specific doctor in handling patient beliefs [11].

Transdermal patches distribute the medicine via the skin in a well-ordered and programmed method in order to rise the medicinal effectiveness of drug. Transdermal patch comprising drugs with diverse proportions of polymeric mixtures and variable plasticizer collections were arranged. It delivers the medicine through skin by well-known circulation at a programmed pace over a long period with a particular amount of dosage. Achievement of a transdermal patch rely on a type of physiological, biological, biophysical and biochemical features. It relies on the constitution, reliability and thickness of the sectioned cornea. The physiology and dimension of the constituents are the sign for diffusion. It rely on the porosity of the membrane in the transdermal medicine distribution system, level of hydration for skin pH and all other physiochemical medicinal features [12].

## 2. Method of formulation:

Transdermal patches that contain Desloratadine were by the solvent casting process. HPMC 6 cps in opted proportion were loaded and diffuse in solvent solution of ethanol and DCM with the proportion of 2:1. The plasticizer was mixed to the polymeric solution and stir it uniformly for 30 min by the help of magnetic stirrer. Ultimately, the drug was subjected with uninterrupted mixing. The patches were formulated through framing the medicine occupied with full of polymeric

solution in a petri plate. The forming solution was dry at normal temperature for a duration of 12 hrs. Formerly the patches were partitioned into 1x1 cm. The dry patches were filled in aluminium foil and kept in desiccators for further study. Few of the features of transdermal patches are listed below:

### *2.1 Physical presence:*

Among all transdermal patches, visual demonstration of colour, clarity, smoothness and flexibility is done.

### *2.2 Thickness of the patch:*

The width of patches was examined at three different spaces via a micrometre and average value were estimated. A minor film strip of dimension 40 x 15 mm was utilizing. Single end of the band was static among sticky tape to provide sustenance to the film once positioned in the film container. Additional end of the films was static among the sticky tape with a small sized pin inserted in the middle of them to retain the strip balanced even though after stretching. A small cavity was incorporated inside the sticky tape close to the pin in which a knob was introduced. A strand was knotted to this hook, distributed above pulley and a minor pin fitted to another end for weight handling purpose. A minor indicator was fitted with the thread that movement above chart paper attached on the bottom plate. To define the flexible power, the film was dragged through pulley organization. Loads were progressively attached to the pan to proliferate the pulling strength until the film was destroyed and the amount of load required to break the film is known as break force.

### *2.3 Solubility of Transdermal patches constituents:*

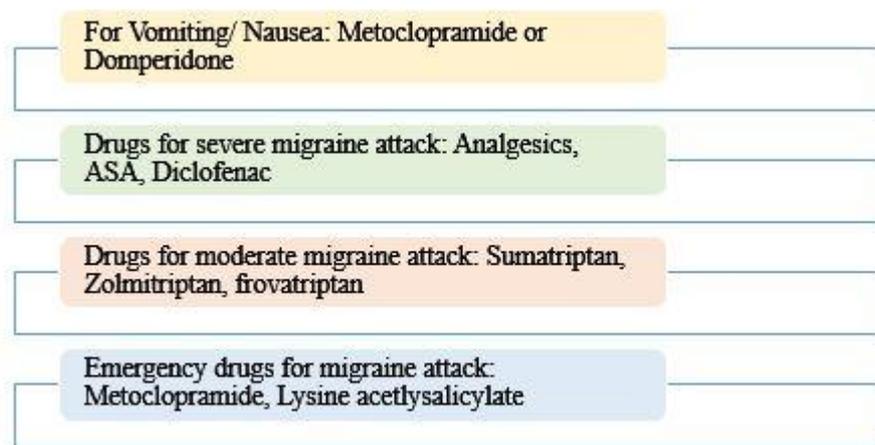
The solubility of triptans was verified in numerous diluents, 10mg of the medicine was liquify in 10ml of respective diluents at normal temperature. The solubility can be best described by its visual observation.

### *2.4 Drug content examination:*

The patches were divided and attached to a destroyer comprising 100 mL of saline phosphate buffer with pH 7.4. The preparation media was mixed with magnetic beads. The substances were sieved by means of Whatman filter paper 1 and the permeate was inspected for the medicine content in contradiction of the source solution comprising of dummy films without drug at 243.5 nm wavelength in spectrophotometer. Injectable triptans could be related as per injection-place annoyance and ache with amplified antagonistic actions like- chest and neck uneasiness, hot mental state, faintness, sleepiness, amplified sickness, and paraesthesia when equated with another type distribution system. These opposing actions may be so acute that migraine patients get hesitated on using the drug or might delay of taking the medicine.

Furthermore, nasally distributed triptans depend on gastric absorption on minor extent due to consuming a major amount of the medicine that pipes down the earlier nasal opening. This may show difficult for individual migraineurs who experiences sickness or gastric immobility by their outbreaks. Significantly, few patients do not appear to agree nasal sprays for the cure of a migraine. Current improvements in medicine distribution system display that a novel migraine blotch may discourse various among these anxieties for patients. The transdermal patches provide the migraine patient various clinical advantages comprising a suitable, non-invasive distribution of medicine that avoids the digestive tract and hepatic first-pass breakdown. This distribution may demonstrate to be the way of optimal for migraine patients facing signs constant with digestive disorder related with a migraine. The defensive role of human skin control physicochemical boundaries to the type of porous material that can go across the obstacles. For a medicine to be

distributed inertly through the skin it requires to have suitable lipophilicity and molecular weight (Figure 2) [13].



**Figure 2: General Medication for the Treatment of Migraine Attack (Acute, Moderate, Emergency and Vomiting Condition)**

Patients specified that want to see all these types of drugs that get dissolved in mouth without the need of any extra fluid. By taking individual patient opinion into consideration while manufacturing suggesting choices is probably to enhance passivity with cure and rise patient fulfilment with the cure given [14].

### LITERATURE REVIEW

Mark W. Pierce [15] found that existing sumatriptan preparations that can be taken orally, through nasal cavity, or under the skin could be related with confinement that can at last result in delay in patient treatment or escaping treatment. Limitations for oral drug formulation are trouble for intake of drug because of vomiting and nausea that are often seen with migraine and unpredictable abortion while nasal and beneath the skin medicine formulation can be accompanied with less bioavailability and an adverse proportion of antagonistic events, respectively. Transdermal drug delivery formulation is an alternative approach for the treatment of migraine specially iontophoresis. It has a better application than all of the present formulation methods to avoid digestive tract, checked and constant distribution, and appropriate intake of drug. One of the most generally recommended migraine treatments is Sumatriptan and recommends one additional treatment device for migraineurs like Zelrix iontophoretic patch.

E. Anne MacGregor et al. [1] described from the former epidemiological findings, that several migraine patients are not consulted with a physician till now. Irrespective of the degree of infirmity, many migraine patients are consuming normal analgesics to treat their severe migraine attack in bed rest condition. Patients want a treatment that show high effectiveness and can perform rapid action and can be dissolved easily when administered orally and for this a new zolmitriptan preparation is most suitable preparation and best route administered method. Barriers for care of migraine patients are that they are not able to consult doctors for treatment and analysis, also they are not getting proper diagnosis for headache and also proper treatment is not provided on the basis of the degree of severity of migraine. Majority of people felt that migraineurs are not getting proper awareness according to the requirement.

Darshan G. Trivedi et al. [8] elaborate that the patches developed were suitable in form of their appearance, width, variation in weight, folding stamina, amount of moisture, tensile ability, break percentage for elongation, and drug content percentage. An oral introduction, can create various antagonistic effects like fatigue, nose or throat, nausea, vomiting, headache etc. And is not a good

candidate for its water solubility property, so shows dissolution level partial absorption. For avoiding these problems, we need a matrix type transdermal patch i.e., Desloratadine which can be prepared by using solvent evaporation method. It was prepared by using film developing polymer like HPMC 6 cps with a plasticizer PG through solvent evaporation method. The developed patches are more suitable in the field of their physicochemical features such as visual representation, width, folding stamina, amount of moisture content, break percentage for elongation, and amount of drug content.

Jerome Goldstein et al. [16] demonstrated that the very first and only transdermal medication available for migraine is Sumatriptan iontophoretic transdermal system, which can be used one time with its application on the upper arm or thigh of the patient and can be disposed after use. On comparison with the migraineurs with placebo with the patients treated by the sumatriptan iontophoretic transdermal method enlightened that they get relief from headache, free from nausea and other migraine-related signs. It provides migraineurs a patient a non-oral way and a non-invasive way to distribute an efficient drug for migraine while it passes through the digestive tract and also overwhelming problems related with digestive signs of migraine. There were no adverse side effect and death is seen in the patients treated with Sumatriptan.

Suneetha Cherukuri et al. [17] demonstrated that TDDS (Transdermal drug delivery systems) was created to assist the discharge and increase the bioavailability of medicine and patient acceptance. From various kinds of transdermal patches, among the various types of transdermal patches, matrix distribution type method dissolves the drug in the solvent with the polymer and further solvent is permitted to evaporate establishing a consistent drug-polymer matrix. The drugs and polymer's physicochemical compatibility was calculated by Fourier transform infrared spectroscopy (FTIR). The patches were more exposed to numerous physical estimation with outside permeation findings using ear skin of pig. TPM, a transdermal patches were organized by matrix kind solvent casting technique to attain a monitored discharge, better-quality bioavailability of the therapeutic medicine and to decrease the harmfulness and found to be an effective drug delivery system as compared with the former reported dose form of TPM [18].

Akila RM et al. [19] mainly concentrated for the improvement, estimation and arithmetical optimization the transdermal patches formed of Almotriptan malate. Almotriptan malate, a transdermal drug used for the treatment of migraine and stated to have the best-persistent pain relief rate with lower side effect rate of all the triptans and therefore creating importance for the development of new path for the therapeutic intake of the drug. Numerous physicochemical factors of the patches were examined. The present study of transdermal patches of Almotriptan malate may offer persistent distribution for long duration for the controlling of migraine, which can be a noble way to avoid the wide hepatic first-pass breakdown. The outcome of the study disclose the possibility of manufacturing rate-controlled transdermal film of Almotriptan Malate for an impactful control and prophylaxis for migraine treatment. More investigations are desired to correlate in vivo and in vitro permeation findings for the manufacturing of suitable Almotriptan malate transdermal system.

Mohamed H. Aboumanei et al. [9] demonstrate the role of Caffeine in the treatment of the migraine which is a naturally present alkaloid compound and can be used in a combination or can be used alone for migraine. The small removal half-life (3–5 h) of caffeine and its association between the absorption from digestive tract and when the digestive tract is empty are the main hurdles to develop an effective oral drug delivery. To prevail such restrictions, caffeine's transdermal proniosomal system was formed. Caffeine suspension that can be intake orally were reported simply in Swiss albino mice. Remarkably, Caffeine in the blood show greater directing capability to the brain than Caffeine suspension that are taken orally. In short, the developed proniosomal method, succeeded in extending the passage time of caffeine in the blood and upgrade its anti-

migraine activity when compared with oral caffeine suspension. It is imagined that transdermal proniosomal method of caffeine can overwhelmed problems related with oral distribution of caffeine. To attain this objective, manufacturing of transdermal proniosomal method of caffeine was done by using concertation phase separation technique.

## DISCUSSION

International Headache Society studies, Migraine is a restricting neurological disorder which cannot be easily diagnosed frequently and is attached with the symptoms involved recurring outbreaks of moderate to acute head pain. It is one of the utmost restricting disorder in the world and is the primary cause of infirmity amongst all neurological diseases. Due to the severances of migraine outbreaks, migraine cures require to take assistance to patients rapidly and securely. Current improvements in the manufacturing of transdermal medicine distribution for cure of migraine show promising response [20]. The atomic descriptions of TPM were exposed that the preparing's prepared by carbopol and ethyl-cellulose were seems to be non-uniform in drug delivery. In atomic pictures of formulations prepared from CAP, superficial morphology was noble in lower concentration.

The usage of triptans in the cure of migraine was a major discovery. Their discriminating sceptical actions at serotonin receptor has delivered visions into the pathophysiological study of migraine and signified a major advance in migraine pharmacotherapy treatment. Sumatriptan was the first manufactured triptans open for medical usage in the United States. Though it transformed the cure of migraine, it proven some disadvantages, like poor oral delivery of drug's bioavailability, unpredictable absorption, and high proportion of headache recurrence. However, the studies are being performed to increase the safety and efficacy of the drugs and also to improve the practical matters such as the experience of the wearer of the patch, and to provide increased duration of action. Other potential improvements include improved transdermal technology that utilizes mechanical energy to increase drug flux across the skin.

Injectable triptans might be associated as per injection-site frustration and headache with enlarged opposed movement's like- uneasiness in chest and neck, mental state disturbance, weakness, drowsiness, enlarged sickness, and paraesthesias once associated with other variety distribution method. These contrasting movements may be so severe that migraineurs get vacillated on consuming the medicine or might show interruption of intake the medicine. Also, nasally spread triptans rely on abdominal absorption on slight extent due to intake a major volume of the drug that channels down the previous nasal opening. This may be demonstrated problematic for specific migraineurs who experience illness or stomach immobility by their outbreaks of migraine. Using other routes for triptans' consumption in count to planning suitable preparations, were effective methods. Present enhancements in medicine delivery method show that a new migraine strap may address numerous amongst these worries for migraineurs. The transdermal patches deliver the migraine patients numerous medical gains encompassing an appropriate, non-invasive delivery of medicine that eludes the gastral tract and hepatic first-pass breakdown. This delivery may verify to be the mode of best for migraine patient fronting signs and symptoms persistent with gastric disorder associated with a migraine.

Though, advance surveys should be accompanied to start their bioavailability and in vitro- in vivo association study are also mandatory, to approve the possible of the intended preparations for usage in humans, henceforth new effective triptans' preparations may seem on the global market in the near upcoming. In modern periods, skin deliberated as a not dangerous port for drug administration, to provide continuous drug release. Patients specified that want to see all these categories of medicines that get melted in oral cavity without the necessity of any additional liquid. By captivating specific patient view into thought while developing proposing varieties is possibly

to improve inactiveness with cure and increase in patient accomplishment with the treatment provided.

## CONCLUSION

Migraine is studied as 3<sup>rd</sup> greatest main disorder worldwide known and among at seventh extreme communal overwhelming illness. Unfortunately our awareness of the pathophysiological disease is partial[3]. Approx. 90% of migraine patients accepted with the declarations that migraine is a furthestmost acute disease than determined individuals understands and the similar individuals does not have awareness of the variance among migraine disorder and normal headache. A Migraine is a mostly headache disorder involving of mild to high magnitude of headache associated with few combinations of severe disability and neuro-autonomic disease like explicit or other ranges of nature, digestive steadiness, poor absorption next to the minor bowel, illness, vomiting, faintness that get poorer with movement, photophobia, and sonophobia. Injectable triptans might be connected as for every injection-site irritation and headache with enlarged incompatible activities like- uneasiness in chest and neck, abnormal mental state, weakness, tiredness, improved sickness, and paraesthesias when associated with other variety distribution method.

But the findings are being executed to rise the security and effectiveness of the medicines and also to increase the applied problems like the know-how of the wearer of the patch, and to deliver amplified period of action. Additional possible enhancements comprise a better transdermal technology that uses automated energy to rise medicine fluidity across the skin. Using other ways for triptans' direction in calculation to scheming suitable preparations, were fruitful methodologies. Though, advance studies should be accompanied to begin their bioavailability and in vitro- in vivo association findings are also mandatory, to approve the impending of the intended preparations for usage in humans, hereafter new effectual triptans' preparations may seem on the market globally in the nearby future. In current periods, skin deliberated as a harmless port for drug consumption, to deliver nonstop drug discharge. Specified Patients wanted to perceive all these varieties of medicines that easily get melted in mouth deprived of the necessity of any extra fluid. By taking specific patient opinions in attention though developed suggesting selections is undoubtedly to boost inactiveness with treatment and increase patient completion with the medication given. Transdermal patches are not very frequently used by the migraineurs because of less understanding about it and irritation on skin due to its regular use. Availability of the transdermal patches known is very rare in remote areas and cost of treatment trough transdermal is not very affordable. Transdermal patches can also be used to reduce the pain during delivery and also can be used to administer hormones in polycystic ovarian syndrome, thyroid and insulin.

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