Investigating the Permeation of Methylphenidate and Rivastigmine using Various Enhancer Groups

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Abstract

The stratum corneum serves as the most challenging obstacle to the transportation of drugs through the skin due to its structure of flattened corneocytes in a lipid-rich matrix. Chemical permeation enhancers assist with this restricted drug delivery, as they react and interact with the stratum corneum and drug to improve diffusion. In this study, improved permeation of methylphenidate, a medication that primarily treats attention-deficit/hyperactivity (ADHD), and rivastigmine, a drug that primarily treats Alzheimer's disease, was analyzed using various enhancer groups to determine the most effective group. Focus was placed on the effects of enhancers on the stratum corneum and the changes it resulted in. Through a systematic review, previously published literature and articles were analyzed and evaluated. Results showed that the alcohol group resulted in the highest solubility average with the enhancer ethanol and the highest permeation coefficient with Transcutol, indicating that alcohol is a viable option for the improved permeation of rivastigmine and methylphenidate.

Keywords: transdermal drug delivery, chemical permeation enhancers, methylphenidate, rivastigmine, stratum corneum

Introduction and Background

Transdermal drug delivery is the transportation of drugs through the skin and into the bloodstream. However, the range of drugs available to this system is restricted, as the skin serves as an effective barrier to external materials such as microorganisms, toxins, and ultraviolet

radiation. Among the skin layers, the outermost layer, known as the stratum corneum, works as the main limitation to permeation. Due to its rigid structure, it restricts penetration to drugs with specific conditions, including a maximum molecular weight of 1 kilodalton (kDa), high lipophilicity, a certain polarity, and non-ionized molecules (Münch et al., 2017).

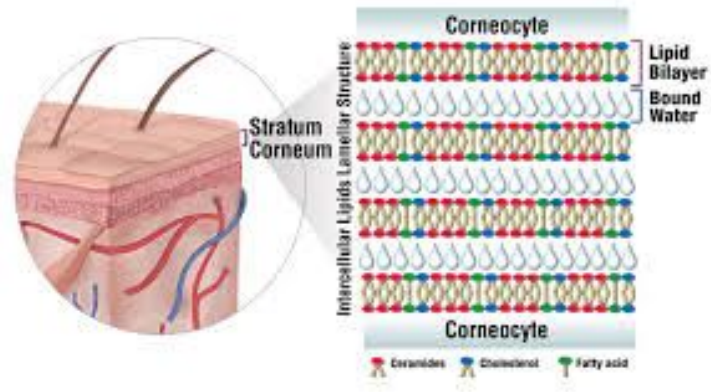

Figure 1. Structure of the stratum corneum. Hydrophobic heads are shown in red, blue, and green, while hydrophilic tails are shown in yellow (Veterinary Team Brief, 2017).

Stratum Corneum and Pathways

The stratum corneum structure consists of 10-15 layers of keratin-rich corneocytes embedded in a lipid matrix composed of ceramides, cholesterols, cholesterol esters, and fatty acids (Fig 1) (Münch et al., 2017; Sakdiset et al., 2017; Schoellhammer et al., 2014). It is often described as having a "brick and mortar" structure due to the long, tile-like shape of the corneocytes (Moghadam et al., 2013; Schoellhammer et al., 2014). Drug delivery through this area, named the transdermal route, entails transport through the intercellular and intracellular pathways. The intercellular pathway requires diffusion around the corneocytes, where the

substance must weave in and out through repeated domains (Fig 2) (Prausnitz and Langer, 2017; Rastogi and Yadav, 2012). It is generally accepted as the most common path for drugs. On the other hand, the intracellular route involves advancing straight through the lipid matrix and corneocytes, causing it to be highly restricted due to the lipid bilayers' structural and solubility conditions (Fig 2) (Prausnitz and Langer, 2017; Rastogi and Yadav, 2012). A previous study on transdermal drug delivery revealed that this section provides the only continuous passage from the surface to the base of the stratum corneum and exists as multilamellar sheets (Rastogi and Yadav, 2012).

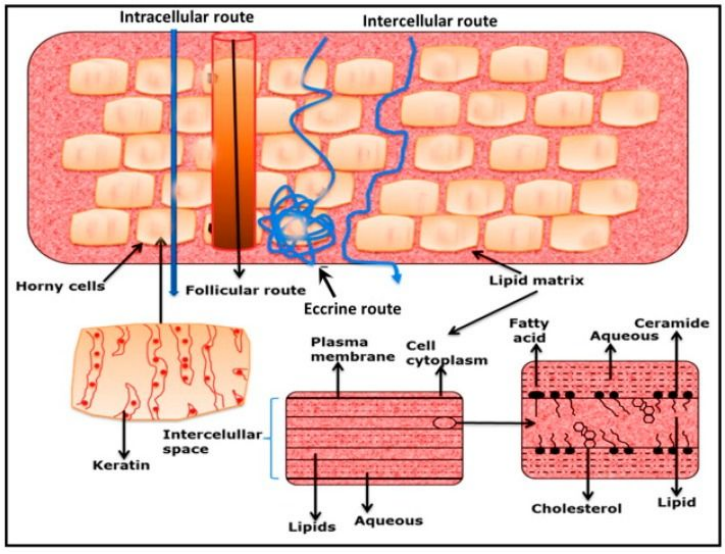

Figure 2. Delivery of drugs via the transepidermal pathway, consisting of the intracellular and intercellular routes. Substance moves directly through the lipid matrix via the intracellular route and weaves in and out via the intercellular route (Alkilani et al., 2015).

Developments in Transdermal Drug Delivery

There are currently nineteen drugs that use FDA-approved transdermal systems. Developments in these systems are classified into three generations of systems: first, second, and third.

First Generation

First generation systems involve the patches clinically used today, such as the nicotine, motion sickness, and hormonal patches (Table 1) (Wilson, 2017). They were initially studied extensively, but it was not until 1904 that the permeability of the skin to allow drug absorption was studied. The development of topical products ensued, with the first report of clinically managing a systemic condition by Bernhard Zondek, a gynecologist who developed the first reliable pregnancy test (Pastore et al., 2015). Focus was placed on the delivery device and the effects of dose, area, and vehicle. Ten years after this, a rate-controlling membrane for steady drug delivery was used on a patient for the first time (Pastore et al., 2015). Subsequently, current patches in clinical use began entering the market. The first was the Scopolamine (hyoscine) patch for the treatment of motion sickness in 1979. A decade later, the first transdermal blockbuster, nicotine patches, was developed, leading to the wide acceptance of transdermal drug delivery. Today, there are a variety of drugs that use transdermal drug patches. Between 2003-2007, the rate of approved patches tripled resulting in a new patch every 7.5 months, compared to only one new patch every 2.2 years in 1979-2002. (Prausnitz and Langer, 2008).

Figure 3. Diagram of the parts of a transdermal patch, developed in the first generation of transdermal drug delivery systems (FDA, 2009).

Methylphenidate is a drug commercially used as a first generation patch that specifically treats attention-deficit/hyperactivity (ADHD) and narcolepsy. Its main action is the elevation of dopamine and norepinephrine, as it is a central nervous system stimulant (Luethi et al, 2017). Another drug, rivastigmine, acts on dementia and Alzheimer's disease as a cognition-enhancing medication (Kurz et al., 2009; Patrick et al., 2009). It is a cholinesterase inhibitor that restrains both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) in the brain (Emre et al., 2010). The illnesses that these two drugs treat are very common, as it has been reported that the frequency of ADHD in children reaches about 10% and the prevalence of dementia reaches as high as 40% in the elderly (Ekmeci et al., 2017; Karci et al., 2017). This conveys the importance of methylphenidate and rivastigmine.

Table 1. List of FDA approved drugs for transdermal drug delivery (Wilson, 2017).

Year	Generic (Brand) Names	Indication
1979	Scopolamine (Transderm Scop®)	Motion sickness
1984	Clonidine (Catapress TTS®)	Hypertension
1986	Estradiol (Estraderm®)	Menopausal symptoms
1990	Fentanyl (Duragesic®)	Chronic pain
1991	Nicotine (Nicoderm®, Habitrol®, Prostep®)	Smoking cessation
1993	Testosterone (Androderm®)	Testosterone deficiency
1995	*Lidocaine/epinephrine (Iontocaine®)*	Local dermal analgesia
1998	Estradiol/norethindrone (Combipatch®)	Menopausal symptoms
1999	Lidocaine (Lidoderm®)	Post-herpetic neuralgia pain
2001	Ethinyl estradiol/norelgestromin (OrthoEvra®)	Contraception
2003	Estradiol/levonorgestrel (Climara Pro®)	Menopause
2003	Oxybutynin (Oxytrol®)	Overactive bladder
2004	*Lidocaine/ultrasound (SonoPrep®)*	Local dermal anesthesia
2005	Lidocaine/tetracaine (Synera®)	Local dermal analgesia
2006	*Fentanyl/iontophoresis (Ionsys®)***	Acute postoperative pain
2006	Methylphenidate (Daytrana®)	ADHD
2006	Selegiline (Emsam®)	Depression
2007	Rotigotine (Neupro®)**	Parkinson's disease
2007	Rivastigmine (Exelon®)	Dementia
2008	Granisetron (Sancuso®)	Chemo-induced emesis
2009	*Oxybutynin (Gelnique®)*	Overactive bladder
2010	Buprenorphine (Butrans®)	Chronic pain

Second Generation

The second generation focuses on enhancing permeation to expand the range of available drugs to transdermal delivery systems. Enhancement techniques developed during this generation consist of chemical permeation enhancers and include the addition of physical methods, such as iontophoresis, the application of a low-current voltage, ablative lasers, the use of an intense wavelength of light, and non-cavitational ultrasound, a pressure wave at a frequency too high for human ears (Munch et al., 2017; Prausnitz and Langer, 2008; Puri et al., 2017; Schoellhammer et al., 2014).

Third Generation

Third generation transdermal drug delivery systems, the most current generation, continue to focus on enhancing permeation but is more specific with targeting the stratum corneum, as it had been established that this layer primarily limits permeation. These systems include many physical techniques, such as: electroporation, cavitational ultrasound (as opposed to non-cavitational), microneedles, thermal ablation, and microdermabrasion. This generation also encompasses combinations of chemical permeation enhancers introduced in the second generation and biochemical enhancers, such as peptides (Munch et al., 2017; Prausnitz and Langer, 2008; Schoellhammer et al., 2014).

Chemical Enhancers

Chemical permeation enhancers interact with the stratum corneum layer to temporarily increase permeation through the corneocyte layer and are currently the most widely studied approach. They do this through a variety of mechanisms. Some enhancers disrupt the highly ordered lipid structure by placing amphiphilic molecules between the proteins, causing the extraction of lipids to result in a packing interruption (Prausnitz and Langer, 2008). Other chemical enhancers interact with the aqueous realm of the bilayer to increase the solubility of drugs (Kumar et al., 2014). This process can be summarized in four points: 1. Modification of the stratum corneum lipid domains to increase fluidity and reduce the resistance of the lipid bilayers 2. Increasing solubility of drugs 3. Disruption effect on the chains of lipids 4. Separation of lipids to create pores or establishment of a drug reservoir in the stratum corneum itself (Moghadam et al., 2013; William and Barry, 2004). They can also be combined together to

increase the effect, as their mechanisms can work synergistically and additively, or added to a physical method to aid it. However, there must be a balance between permeability and safety, as chemical permeation enhancers can cause skin irritation or cytotoxicity. A general guideline of principles a chemical enhancer should follow is as followed (Kumar et al., 2014; William and Barry, 2004):

- They should be non-irritating, non-toxic, and non-allergenic.
- They should work quickly and the effect should be reproducible and anticipated.
- They should have no pharmacological activity in the body.
- They should work only in one direction. They cannot promote diffusion out of the skin.
- Their effects should be reversible. When they are removed, the skin's barrier properties must return quickly and entirely.
- They must be cosmetically acceptable with an appropriate skin "feel."

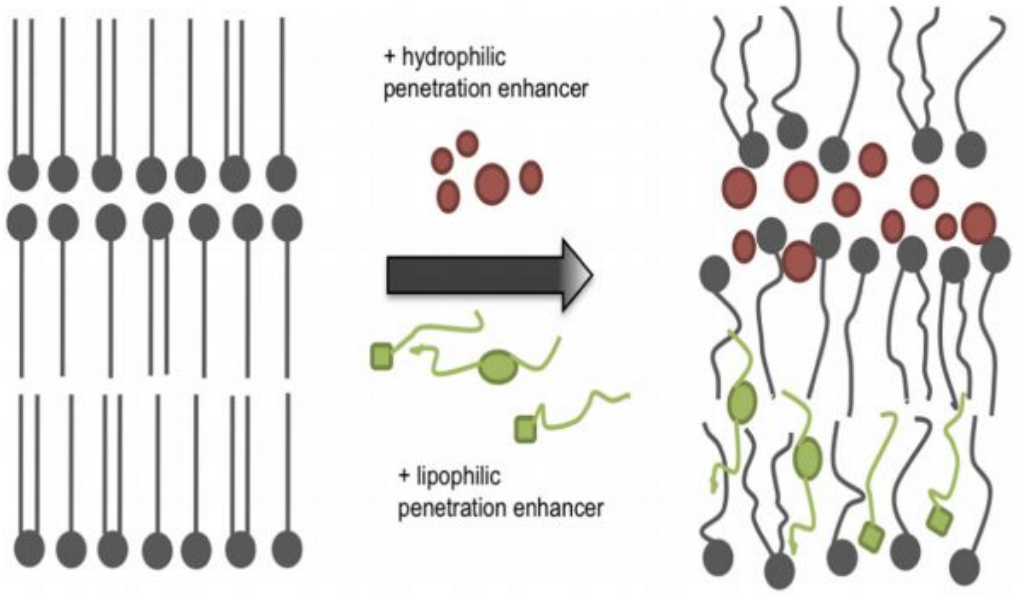

Figure 4. Representation of the penetration through the stratum corneum lipid matrix and the possible ways of interaction with hydrophilic and lipophilic chemical permeation enhancers (Münch et al., 2017).

Chemical Enhancer Groups

These enhancers are classified into groups based on their chemical structures, and not on mechanisms or effects on the skin. Accordingly, each chemical enhancer in a group may affect the stratum corneum differently.

Alcohols

Alcohols possess a variety of effects, such as: disruption of stratum corneum lipid bilayers, increasing drug solubility, and alteration of the tissue's solvent nature. It has also been speculated that the quick diffusion of these chemicals, specifically ethanol, results in a supersaturated solution with a larger driving force for permeation. Furthermore, some enhancers are known to be miscible with both hydrophobic and hydrophilic formulations. This group

encompasses alkanols, alkenols, ethylene glycols, polyethylene glycols, and glycerols and includes the enhancers ethanol, Transcutol, propylene glycol, myristyl alcohol, lauryl alcohol, and oleyl alcohol. It is the most frequently used enhancer group (Ameen and Kohn, 2017; Karande and Mitragotri, 2009; Williams and Barry; 2004).

Water

Increased stratum corneum hydration usually results in the increased permeation of drugs, as water increases solubility. Excessive water content causes pore pathways in the stratum corneum lipid bilayers to swell and connect, creating a continuous pathway for drugs to permeate through (Williams and Barry; 2004).

Fatty Acids

Drugs have been permeated by a number of fatty acids, such as oleic acid, lauric acid, citric acid, linoleic acid, palmitic acid, and myristic acid. Their mechanisms include diffusing into lipid domains and modifying them to increase fluidity and the creation of separate lipid domain, known as pools, in the lipid bilayers to cause disruption (Karande and Mitragotri, 2009; Lane, 2013; Williams and Barry; 2004).

Fatty Acid Esters

The esters of fatty acids are a group of their own, as they improve permeation for a variety of drugs. These enhancers induce diffusion by disrupting the ordered lipid domains. Isopropyl myristate is the most widely studied ester, but there are a range of other chemical enhancers in this group that have been used commercially, such as ethyl oleate, glyceryl monolaurate, lauryl lactate, methyl oleate, oleyl oleate, isopropyl palmitate, and propylene glycol monolaurate (Karande and Mitragotri, 2009; Lane, 2013).

Surfactants

Much of the studied surfactants have been used in cosmetics and therapeutic substances. These include anionic, cationic, zwitterionic and non-ionic surfactants, with most studies focusing on the anionic and non-ionic categories. This groups' effects differ with the balance between hydrophilic and lipophilic, charge, and the length of the lipid tail and include increasing stratum corneum fluidity by destructuring lipids. However, their safety poses an issue, as anionic and cationic surfactants have the capability to induce damage to the human skin. This group includes Tween-80, sodium lauryl sulfate, methylammonium bromide, benzalkonium chloride, and cetylpyridinium chloride (Karande and Mitragotri, 2009; Lane, 2013; Williams and Barry; 2004).

Sulfoxides

These chemicals are known to interact with proteins and modify stratum corneum lipid domains, creating drug "reservoirs" in the process. Most are concentration dependent, due to their increased effectiveness at high concentrations. This poses a problem, as most sulfoxides result in erythema and denature proteins at such concentrations. Many of these enhancers are related to dimethyl sulfoxide, one of the earliest chemicals to be studied as a chemical permeation enhancer, as it is very effective. However, dimethyl sulfoxide variants result in irreversible damage at high concentrations. They include dimethylacetamide, dimethylformamide, and decyl methyl sulfoxide (Lane, 2013; Williams and Barry; 2004).

Amides

Including pyrrolidones, such as N-methylpyrrolidone and 2-pyrrolidone, and Azone, this group partitions into the stratum corneum and modifies the solvent nature of the layers, disrupts

the ordered lipid packing, and creates drug "reservoirs." This creates the potential for drug release over an extended time. Moreover, there have been reports of erythema and toxic hygroscopic contact with the use of pyrrolidones (Lane, 2013; Williams and Barry; 2004).

Azone is the first synthetically designed permeation enhancer, extensively studied in the 1980s and 1990s. It has a similar structure as dimethyl sulfoxide, but lacks the aprotic sulfoxide group that makes it harmful. This allows it to directly interact with stratum corneum lipids to increase fluidity. Furthermore, it is also concentration dependent, but unlike sulfoxides, they are more effective at low concentrations. Despite its large potential as a chemical permeation enhancer for drugs, it has never been used commercially (Lane, 2013; Williams and Barry; 2004).

Terpenes, terpenoids, essential oils

This group's effects rely on the skin's exact physicochemical properties and includes: changing the solvent nature of the stratum corneum, disrupting the lipid domains, and the creation of separate domains. These effects' longevity depends on the size of the enhancer, as smaller chemicals wash out of the stratum corneum more quickly than large ones. However, there is not enough research on this group, so it is unknown if it is capable of increasing drug diffusion in human skin. Chemical enhancers limonene, menthol, carveol, carvone, 1,8-cineole, nerolidol, and eugenol are included in this category (Karande and Mitragotri, 2009; Lane, 2013; Williams and Barry; 2004).

Chemical Enhancer Safety

The effect of these chemical enhancers is limited by the possibility of causing skin irritation. This is characterized by unfavorable or harmful effects as a result of the interaction between chemical enhancer and skin and may include: erythema, swelling, inflammation, dermatitis, and even excess transepidermal water loss (TEWL) (Karande and Mitragotri, 2009). For the majority of enhancers, their potential to cause harm relies heavily on their concentrations and potency. Enhancers at high concentrations and potency are more likely to cause irritation, as they are very effective at disrupting and modifying the stratum corneum. They also may result in more drastic effects, such as: the exposure of lipid domains, the disruption of corneocytes, and the formation of vacuoles. More severe situations entail the permeation of such chemical enhancers into the skin layer right below the stratum corneum, known as the epidermis. They can interact with keratinocytes, the living cells of the skin, and result in cytotoxicity (Karande and Mitragotri, 2009; Williams and Barry; 2004). Exceptions to this include Azone and ethanol, as they have more activity at low concentrations, allowing them to avoid the risk of damage. Evidently, there must be a balance between permeability and safety, as chemical permeation enhancers can cause skin irritation or cytotoxicity (Kumar et al., 2014; William and Barry, 2004).

Benefits and Advantages

Transdermal drug delivery systems avoid the many risks traditional methods possess and have many advantages. This allows for higher patient compliance, as oral administration is often difficult and uncomfortable and 30% of adults suffer from needle phobia (Schoellhammer et al.,

2014). Furthermore, transdermal drug delivery systems avoid the first-pass effect of the liver and certain dangers, such as the spread of disease through needle reuse and the creation of harmful medical waste. In the United States alone, almost 800,000 cases of needle injuries from medical professionals are reported every year (Schoellhammer et al., 2014). This results in the necessity of further treatment, and therefore more expenses. On another note, transdermal delivery systems can be self-administered and provide controlled release of medication, eliminating the risk of overdose (Munch et al., 2017; Prausnitz and Langer, 2008; Puri et al., 2017).

This research study is thus a step towards improving and enhancing the permeation of methylphenidate and rivastigmine in the stratum corneum. With more effective delivery of these medications, traditional methods will no longer be used as often, allowing for the avoidance of their disadvantages and negative effects. This investigation examined the most commonly studied chemical enhancers: oleic acid, isopropyl myristate, Transcutol, dimethyl sulfoxide, N-methylpyrrolidone, ethanol, propylene, and Tween-80, as well as the most commonly studied mechanism: the increase of drug solubility.

Purpose

The purpose of this study is to investigate the effect of various chemical enhancer groups on the permeation of methylphenidate and rivastigmine and includes disclosing the most effective enhancer group for the diffusion these two drugs. Enhanced permeation of methylphenidate and rivastigmine will allow for more people to use transdermal drug delivery systems with such medications, thus avoiding the disadvantages of traditional methods and

increasing patient compliance. To achieve this goal, it was necessary to study and analyze chemical permeation enhancers, the mechanisms by which they improve permeability, and the effects they have on the stratum corneum. This includes the increase of drug solubility and permeation coefficients. Furthermore, there are currently no or very few systematic reviews studying the improved permeation of drugs with chemical enhancers.

Research Question

Focus was placed on discovering the most effective chemical enhancer group for enhanced permeation of methylphenidate and rivastigmine, medications for common illnesses. Therefore, the question this study attempted to answer is: which chemical permeation enhancer group will result in the most enhanced permeation of methylphenidate and rivastigmine?

Alternate Hypothesis

Considering that the chemical permeation enhancer group of alcohol is the most widely studied enhancer due to its large range of enhancers, and therefore mechanisms, effects, and characteristics, alcohol is hypothesized to result in the most enhanced diffusion of methylphenidate and rivastigmine.

Null Hypothesis

The chemical permeation enhancer group of alcohol will not result in the most enhanced diffusion of methylphenidate and rivastigmine.

Methods

Data Sources

The research study design is secondary data systematic review. An extensive collection of articles and previously published studies from various online databases, such as PLoS ONE, ScienceDirect, PUBMED-NCBI, and Elsevier, was conducted. Keywords such as “transdermal,” “skin,” “delivery systems,” “drugs,” “permeation,” “chemical permeation enhancer groups,” “chemical enhancer mechanisms,” “stratum corneum,” “rivastigmine,” and “methylphenidate” were used to search for relevant articles.

The data range or time-period for the data collection source is from 1995 to 2017. Much work has been done in the area of transdermal drug delivery in the last three decades, making work before the 1990s outdated and impractical to use to reach a new solution. However, such articles do contain information that provides a strong foundation to the topic, so they have been utilized for background.

This was the most appropriate method for this study because it allows for the opportunity to propose a solution based on previous work. Conducting an experiment to gain data is not necessary. Surveys are not appropriate because it is impossible to conduct on a sufficient amount

of individuals, as not many have used transdermal systems. Secondary data analysis would also not work because there is not one agency or source with the necessary data.

Data Extraction

When papers were examined, it was found that studies generally addressed only one effect on permeation: drug solubility. Accordingly, this paper was limited to studying the solubility of drugs using different chemical permeation enhancers. Studies also recorded permeation coefficients, allowing this study to analyze the correlation between solubility and permeation coefficients.

Search results were also initially skimmed through to record the most commonly studied chemical enhancers. Articles were then obtained based on the chemical enhancer, as they were discarded if they did not include the most common enhancers. However, they were not included in the study if they were published before the 1990s, as their information is now outdated. Some papers were also not available to the public, limiting the size of this study.

Data and Statistical Analysis

Data was originally recorded in data tables using Google Sheets. They were then transferred to Excel to perform statistical analysis, as Google Sheets was missing necessary operations.

Solubility averages, obtained for eight chemical permeation enhancers, using solubility measurements from twelve different studies were calculated using Excel. This set of data was gathered to study an effect of chemical enhancers on permeation. Permeation coefficient

averages, obtained for eight chemical permeation enhancers, using permeation coefficients from fourteen different studies were similarly calculated using Excel. This data set was gathered to observe which chemical enhancer resulted in the highest permeation. Standard deviations of the solubility measurements and permeation coefficients for each chemical permeation enhancer were also calculated using Excel.

Utilizing Excel, two bar graphs were created using the solubility averages and the permeation coefficient averages for eight chemical enhancers. The standard deviations for each chemical enhancer were inputted in both bar graphs to express the extent of deviation of each data set.

Methods of Obtained Articles

Most papers and articles utilized in this study conducted their research with similar methods. Generally, solubility measurements were obtained by adding excess chemical permeation enhancer to a drug formulation. These mixtures were then frequently immersed in a water bath and allowed to reach equilibrium. They were passed through a membrane filter, which was then used to determine concentration with high-performance liquid chromatography (HPLC). Each HPLC system was equipped with varying pumps, automatic injectors, columns, and mobile and stationary phases. The flow rates, however, were consistently 1.0 mL/min. Furthermore, permeation coefficients were obtained by plotting the cumulative amount of drug permeated per unit area against time and calculating the slope, or flux. This flux was then divided with the drug concentration in the donor cell to get the coefficient.

Results

Solubility

The average solubilities of the chemical enhancers oleic acid, isopropyl myristate, Transcutol, dimethyl sulfoxide, N-methylpyrrolidone, ethanol, propylene, and Tween-80 is shown in Table 2. Ethanol resulted in the highest drug solubility at an average of 374.43 mg/mL, significantly greater than the others. Propylene glycol at 90.17 mg/mL followed, while oleic acid and Transcutol resulted in similar solubility averages, resulting in 80.9 mg/mL and 70.4 mg/mL respectively. The averages of dimethyl sulfoxide and N-methylpyrrolidone were found to be 27.77 mg/ml and 23.64 mg/mL. The lowest solubilities were found with isopropyl myristate and Tween-80, with averages of 7.9 mg/mL and 5.88 mg/mL respectively, amounting to about 47 times and 62 times less than ethanol.

Ethanol and propylene glycol, the two chemical enhancers that resulted in the highest solubility, are both included in the alcohol group. Isopropyl myristate is in the chemical enhancer group of esters, while Tween-80 is considered a surfactant.

Table 2: Average solubility (mg/mL) of sample drug formulations with as reported by several researchers (Ameen and Kohn, 2017; Cho and Choi, 1998; Elshafeey et al., 2011; Kikwai et al., 2002; Krishnaiah et al., 2008; Lee and Chun, 2012; Mutalik et al., 2009; Nokhodchi et al., 2002; Prasanthi and Lakshmi, 2012; Ren et al., 2008; Shokri et al., 2001; Tuntiyasawasdikul et al., 2014)

Chemical enhancers	**Average drug solubility**	

	(mg/mL)	**Standard Deviation**
Oleic acid	80.9	39.97
Isopropyl Myristate	7.9	8.54
Transcutol	70.4	31.36
Dimethyl sulfoxide	27.77	14.78
N-methylpyrrolidone	23.64	13.56
Ethanol	374.43	189.95
Propylene Glycol	131.53	49.01
Tween-80	5.88	3.46

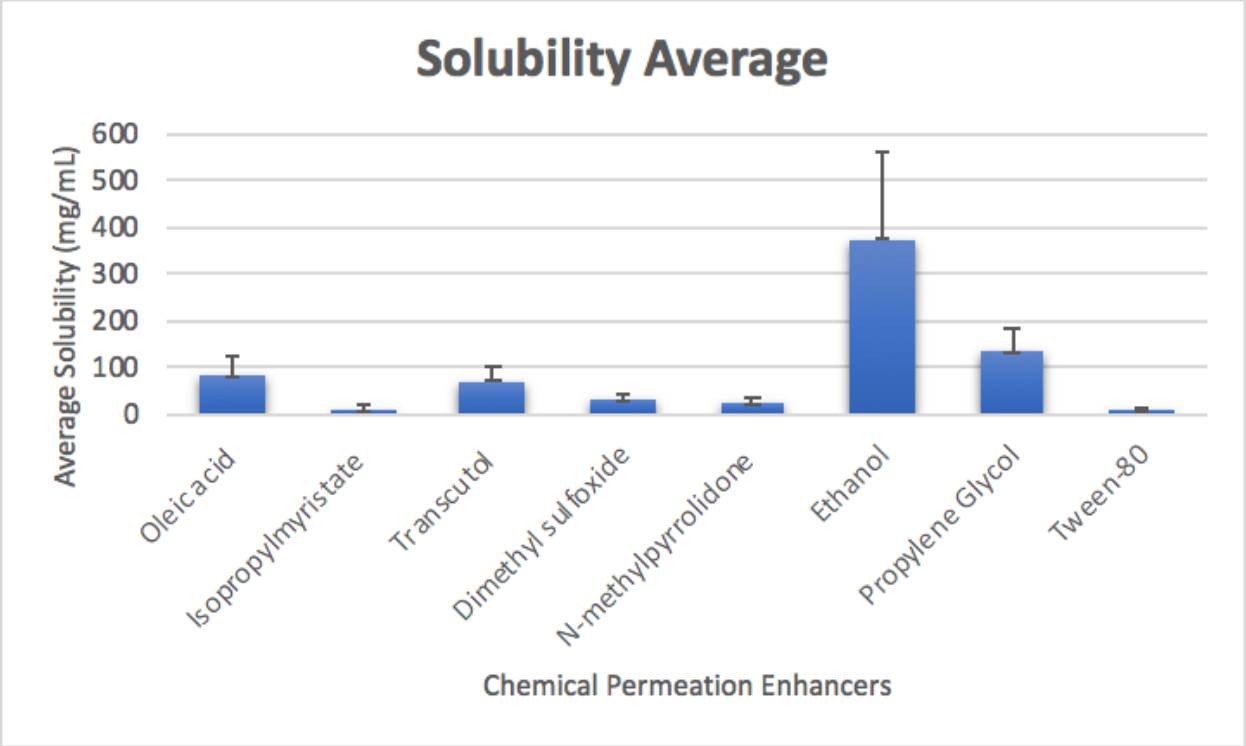

Figure 6. Solubility averages (mg/mL) of drug formulations with various chemical permeation enhancers as reported by several researchers (Ameen and Kohn, 2017; Cho and Choi, 1998; Elshafeey et al., 2011; Kikwai et al., 2002; Krishnaiah et al., 2008; Lee and Chun, 2012; Mutalik et al., 2009; Nokhodchi et al., 2002; Prasanthi and Lakshmi, 2012; Ren et al., 2008; Shokri et al., 2001; Tuntiyasawasdikul et al., 2014)

Permeation Coefficient

Table 3 shows the permeability coefficient averages of oleic acid, isopropyl myristate, Transcutol, dimethyl sulfoxide, N-methylpyrrolidone, ethanol, propylene, and Tween-80. The study revealed that Transcutol possessed the highest permeation coefficient average at 4.38×10^{-3} cm/hr, amounting to about 2.9 times greater than that of the smallest. N-methylpyrrolidone

followed at a coefficient average of $3.94x10^{-3}$ cm/hr, while isopropyl myristate 's average was found to be $3.3x10^{-3}$ cm/hr. Oleic acid and ethanol possessed similar permeation coefficient averages at $2.5x10^{-3}$ cm/hr and $2.13x10^{-3}$ cm/hr respectively. The averages of both dimethyl sulfoxide and propylene glycol were found to be $2x10^{-3}$ cm/hr. The smallest coefficient average was found with Tween-80 at $1.49x10^{-3}$ cm/hr.

The chemical enhancer with the highest permeation coefficient is classified as an alcohol. The following enhancer, N-methylpyrrolidone, however, is part of the amide group. Tween-80 is considered a surfactant.

Table 3. Average permeability coefficient ($x10^{-3}$ cm/hr) of sample drug formulations with chemical enhancers as reported by several researchers (Aboofalezi et al., 2002; Ameen and Kohn, 2017; Ibrahim and Li, 2009; Jung et al., 2013; Kikwai et al., 2002; Krishnaiah et al., 2008; Mutalik et al., 2009; Nair et al., 2017; Nokhodchi et al., 2002; Prasanthi and Lakshmi, 2012; Ren et al., 2008; Santoyo et al., 1995; Shokri et al., 2001; Tuntiyasawasdikul et al., 2014)

Chemical Permeation Enhancer	**Permeability Coefficient Average ($x10^{-3}$ cm/hr)**	**Standard Deviation**
Oleic acid	2.5	0.62
Isopropyl Myristate	3.3	1.82
Transcutol	4.38	2.6

Dimethyl sulfoxide	2	1.11
N-methylpyrrolidone	3.9	2.88
Ethanol	2.13	1.8
Propylene Glycol	2	1.42
Tween-80	1.49	2

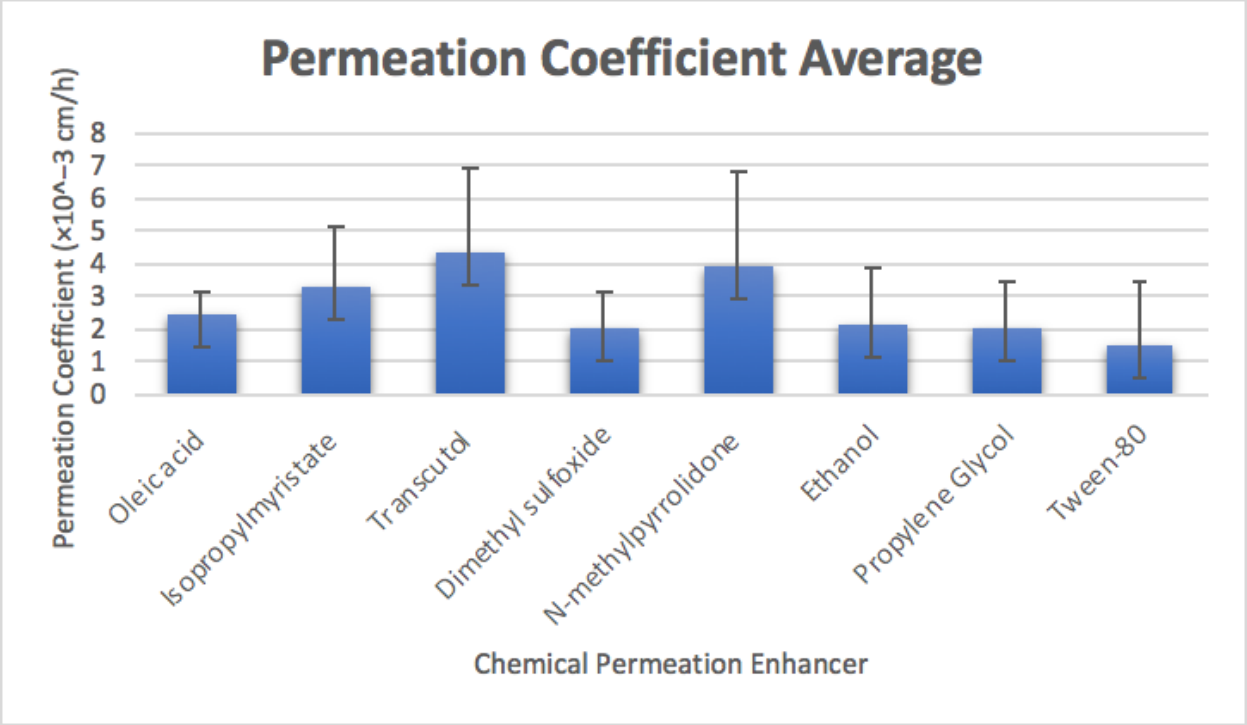

Figure 7. Permeation coefficient averages ($x10^{-3}$ cm/hr) of sample drug formulations with chemical enhancers as reported by several researchers (Aboofalezi et al., 2002; Ameen and Kohn, 2017; Ibrahim and Li, 2009; Jung et al., 2013; Kikwai et al., 2002; Krishnaiah et al., 2008;

Mutalik et al., 2009; Nair et al., 2017; Nokhodchi et al., 2002; Prasanthi and Lakshmi, 2012; Ren et al., 2008; Santoyo et al., 1995; Shokri et al., 2001; Tuntiyasawasdikul et al., 2014)

Discussion

Results show that ethanol resulted in the highest solubility at an average of 374.63 mg/mL, with propylene glycol at 131.53 mg/mL following (Table 2). As both chemical enhancers are considered alcohols, this outcome correlates with the group's most common mechanisms: disruption of stratum corneum lipids, increasing drug solubility, and alteration of the tissue's solvent nature (Karande and Mitragotri, 2009; Williams and Barry; 2004). Similarly, as exhibited in Table 2, isopropyl myristate and Tween-80 resulted in the lowest average solubilities at 7.9 mg/mL and 5.88 mg/mL respectively, due to the fact that their enhancer groups, amides and surfactants, do not commonly improve drug solubility.

Table 3 reveals a lack of correlation with the solubility results in Table 2. It was found that Transcutol resulted in the highest permeation coefficient with an average of 4.38×10^{-3} cm/hr. This enhancer did not result in the highest solubility average, though it is also an alcohol. Moreover, ethanol and propylene glycol, the leading chemical enhancers in the solubility averages, were found to have only adequate permeation coefficients. The inconsistency in the results implies that other mechanisms, such as the modification of lipid domains, significantly impact diffusion. Therefore, along with improving drug solubility, each enhancer affected the stratum corneum in another way to improve permeation. Additionally, the lack of correlation conveys that some mechanisms more heavily affect permeation than others, as shown by

ethanol's solubility average being significantly higher than the other chemical enhancers', but permeation coefficient being two times less than Transcutol's.

Despite the discrepancy between the two data sets, both support the hypothesis that alcohol will result in the most improved permeation of rivastigmine and methylphenidate. This is due to the fact that chemical enhancers part of the alcohol group resulted in the highest solubility and permeation coefficient averages, as presented in Figure 6 and 7. Accordingly, the alcohol group has potential to be the most effective chemical enhancer for the improved permeation of methylphenidate and rivastigmine based on the results of this study. This conclusion also establishes that the alcohol group's various mechanisms, effects, and characteristics allow for its effectiveness in improving permeation.

Safety also has a significant role in determining the feasibility of chemical enhancers, as many have the potential to cause skin irritation such as erythema, inflammation, and swelling. For example, N-methylpyrrolidone, the chemical enhancer that resulted in the second highest permeation coefficient average, is known to induce erythema (Lane, 2013; Williams and Barry, 2004). This makes amides an unreasonable enhancer group to use for the permeation of rivastigmine and methylphenidate. On the contrary, the alcohol group has not been reported to cause any skin irritation. These enhancers, such as ethanol, are known to work better in low concentrations, removing the risk of damage and making alcohol a viable group (Williams and Barry, 2004). This implies that alcohol is a more viable option than the other groups.

Limitations

Due to limited papers available to the public, the number of articles included in this systematic review study is small, making it only feasible to cover the most common chemical enhancer groups and analyze the most commonly studied enhancers. Furthermore, as most of the available studies only observed drug solubility, it was not possible to examine other mechanisms, such as the disruption and modification of lipid bilayers and the alteration of the solvent nature of the stratum corneum.

Conclusion

The alcohol group was shown to result in the highest drug solubility average with the enhancer ethanol and the highest permeation coefficient average with the enhancer Transcutol. These results support the hypothesis that the chemical enhancer group of alcohol will result in the most improved permeation of rivastigmine and methylphenidate, as the data indicates that alcohol is a viable group. Furthermore, there have been no reports of skin irritation with this group, suggesting that possesses a balance between improved permeation and safety.

Further Work

Further research on the mechanisms by which chemical enhancers increase permeation should be done, as drug solubility is just one mechanism of many. This would allow for a wider understanding of the correlation between the effects of chemical enhancers and permeation and give more insight into the many factors that affect improved permeation. Additional investigations would also provide explanations on matters such as why some mechanisms have a

more significant influence on increased permeation than others, further clarifying the reason there was a lack of correlation between the drug solubility averages and permeation coefficient averages. Furthermore, a larger range of chemical enhancers should be examined, as to produce a more precise and thorough study and thus, a more reliable conclusion.

Ultimately, to determine the exact chemical enhancer that will result in the most efficient diffusion, an experiment should be done to test the permeation of methylphenidate and rivastigmine with such enhancers. However, safety must be taken into consideration if it is conducted on human skin, as many chemical enhancers are known to cause damage to the skin.

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