MANUSCRIPT COMBINED DOES DIMETHYL SULFOXIDE(DMSO) ENHANCE TRANSDERMAL DICLOFENAC DRUG DELIVERY FOR POST OPERATIVE PAIN IN MAXILLOFACIAL SURGERY-A RANDOMISED CONTROLLED CLINICAL TRIAL.

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Article History: Received: 12.12.2022 **Revised:** 29.01.2023 **Accepted:** 15.03.2023

ABSTRACT

AIM To assess plasma concentrations of transdermal diclofenac patch (Nupatch) with the aid of Dimethyl Sulfoxide (DMSO) as a chemical skin permeation enhancer in post-operative pain management.

OBJECTIVES:

- To assess the pain levels using Visual analog scale
- To assess plasma levels of diclofenac diethylamineby means of UV-spectrophotometry

RESULTS: The Visual analog scores and the plasma diclofenac concentrations show that the patients from the study group demonstrated increased amounts of plasma dimethyl sulfoxide was used an adjuvant to increase the absorption from the Diclofenac diethylamine 200mg Transdermal patch (Nupatch) shown to have better pain scores and high plasma

CONCLUSION: Chemical permeation enhancer (Dimethyl sulfoxide) as an adjuvant, one of the modalities available. UV spectroscopy studies revealed increased plasma concentrations of drugs (NSAIDS-DICLOFENAC DIETHYLAMINE) for longer duration which facilitate better management of pain helping the patient recover when compared to patients either on transdermal patches alone, oral or I.V drug administration.

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DOI: 10.31838/ecb/2023.12.s2.083

1. Introduction

"Pain" is a highly unbearable experience, and have a devastatingly adverse effect on every other aspect of life, including capacity to function. Poorly managed immediate postoperative pain can lead to complications and increased period of rehabilitation, and has a detrimental effect on all aspects of quality of life. This kind of an impact has been found to be common for every age and type and source of pain in which it has been studied. Post operative pain followed by maxillofacial surgeries is common and the goal is to reduce and/or eliminate pain leading to discomfort with minimum side effects. Though it is possible by several methods, the traditional methods of oral or IV medications have varied side effects.

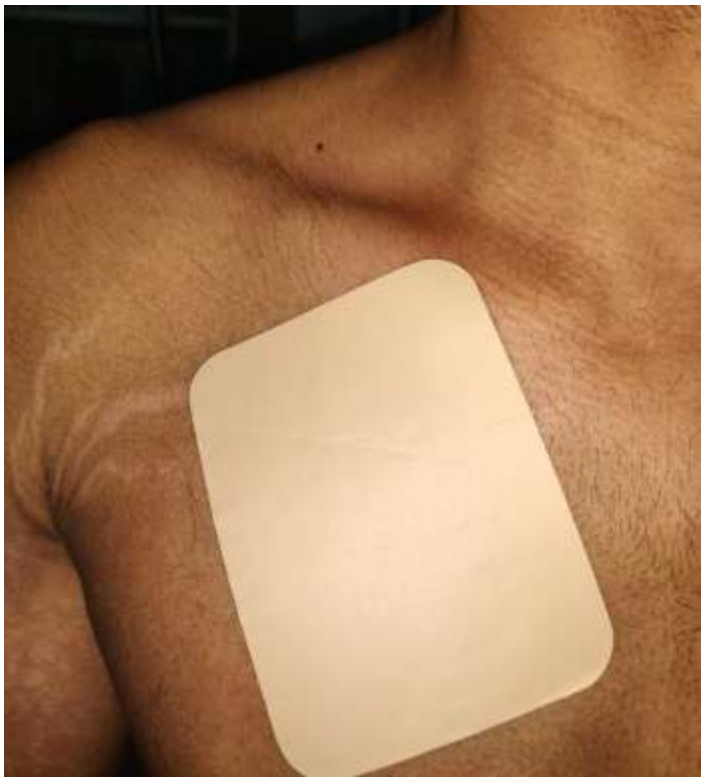
"Oral drug delivery" systems have some limitations such as reduction of drug stability in the GI tract and subjected to "first pass" GI and "Hepatic metabolism". IV route of drug administration has some potential disadvantages, causing pain, and as self-administration Is not possible causing low patient compliance. In order to relieve patient from post-operative pain, transdermal analgesic patches play a major role, But studies indicate that Stratum corneum of the skin acts as a barrier to chemicals and reduces the efficacy of transdermal patches.

Modification of the physiological-properties of the SC (stratum corneum) may lead to "improved permeability" of drugs into the skin[3], by hydration with the use of chemical enhancers as methods for modifying the SC has been explained. Dimethyl sulfoxide is known to be earliest and most widely studied compounds to be used as a penetration enhancer. It facilitates the transdermal delivery of drugs to provide localized and systemic drug delivery through capillary blood circulartion[2]. It is currently used along with topical diclofenac sodium and diclofenac diethylamine formulations.

2. Materials And Methods

SAMPLE SIZE: 24
SAMPLE SIZE CALCULATION DETAILS: Sample size was estimated based on the results of the previous study. The effect size was calculated as 0.58. With 90% power of the study, 5% α error the final sample size was estimated using G*power software, version 3.1.9.7
Number of groups: 2
Source of sample: SRM DENTAL COLLEGE AND HOSPITAL, RAMAPURAM.
Method of sampling: simple random.
METHODOLOGY: Patients undergoing orthognathic surgery within the age group between 14 years to 35 years and patients willing or giving consent for surgery are included in the study and Age group below 14 years and above 35 years and patients not willing for surgery and also with known skin allergies and medically compromised patients have been excluded. 5ml of Blood is withdrawn and stored in EDTA tubes, centrifuged to separate the plasma, and then stored at -20□c until analyzed.

2ml of 60 % DMSO is applied over the non-hairy skin, and a diclofenac transdermal patch (Nupatch) 200 mg is placed on the site of application of DMSO one hour prior to the surgery .



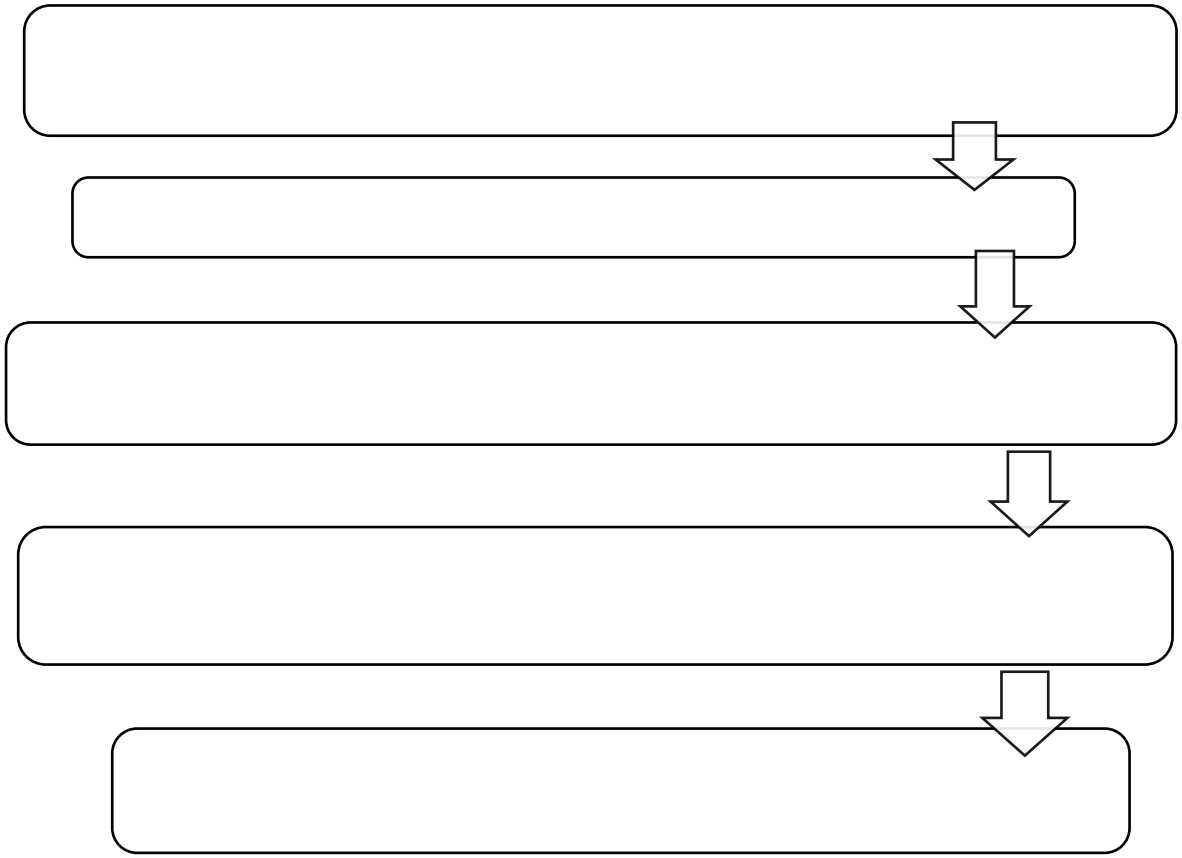
Blood sample is collected after 6 hours from the time of application for UV-spectrophotometry test to assess the plasma concentrations of diclofenac.

One patch is placed every 24 hours and pain is assessed using visual analog scale[24,25,26,27]. Skin at the site of transdermal patch is assessed for any rash or pruritis. Rescue medication (dolo-650) will be given to patients if necessary (VAS score ≥ 5) .

Descriptive statistics of the explanatory and outcome variables will be calculated by mean, quantitative variables by standard deviation, and qualitative variables by frequency and proportion. Chi-Square/Fisher Exact/Fisher Freeman Halton test by cross tabulation will be used to compare frequencies. "Shapiro Wilk test will be used to assess the normality of the data. For normally distributed data statistical difference between two groups will be compared using independent sample t-test. For comparison of more than two groups, "one-way ANOVA with post hoc Tukey's HSD for data meeting the assumption of homogeneity of variances and for data violating the assumption of homogeneity of variances post hoc Games Howell test" will be used.If the data is found to be non-normally distributed comparison of two group will be carried out using Mann Whitney-U test and Kruskal-Wallis test will be applied to check the statistical difference in more than two groups with post-hoc Mann-Whitney for pair-wise comparison. Any p-value less than 0.05 will considered to be significant.

Primary Outcome: Better pain management with minimal complications.

Secondary Outcome: To reduce the dosage of rescue analgesics , and ease the post-operative period.



STATISTICAL ANALYSIS

The Normality tests, Kolmogorov-Smirnov and Shapiro-Wilks tests results reveal the study followed normal distribution. Therefore, to analyse the data, parametric test was applied. Descriptive statistics was expressed using mean and standard deviation. Inferential statistics was done by using independent sample t test/Unpaired t test to find the mean difference between the variables in case and control group. To analyse the data SPSS (IBM SPSS Statistics for Windows, Version 26.0, Armonk, NY: IBM Corp. Released 2019) is used. Significance level is fixed as 5% ($\alpha = 0.05$). P-value <0.05 is considered to be statistically significant.

3. Results

Table 1 shows the descriptive statistics of plasma concentration among the case and control group. The mean was found to be higher in case group (997.17) than the control group (851.58) which implies that clinically plasma concentration was higher in case than in control group. Table 2 shows the mean difference of plasma concentration among the case and control group. P-value <0.05 was considered to be statistically significant. While assessing the difference it showed that statistically significant difference was seen among the case and control group with p-value of 0.001.

Table 3 shows the descriptive statistics of vas score in 2 hours among the case and control group. The pain score was found to be same in case and control group (1.41). This clearly shows clinically they is no difference in the pain score. While assessing statistically, it showed insignificant difference among the case and control group. Table 5 shows the descriptive statistics of vas score in 6 hours among the case and control group. The pain score was found to be higher in control (3.5) than the case group (2.3) which implies clinically pain is seen relatively lower in case group than control group. While assessing statistically, P-value was found to be <0.05 which showed statistically significant difference was seen among the case and control group.

Table 7 shows the descriptive statistics of vas score in 12 hours among the case and control group. The pain score was found to be higher in control (5.08) than the case group (4.25) which showed clinically case group had lesser pain felt. Statistically it was shown difference was seen among the case and control group with P-value of 0.044. Table 9 shows the descriptive statistics of vas score in 24 hours among the case and control group. The mean was found to be higher in control (6.91) than the case group (5.83). while assessing the statistically, the P-value was found to be 0.015 which showed statistically significant difference

was seen among the case and control group during 24 hours of pain assessment using VAS scale[25,26,27.] Table 11 shows the descriptive statistics of efficacy of transdermal patch for 24 hours among the case and control group which showed the efficiency was higher in case group (15.83) than the control group (12.41). This clearly implies that clinically case group was found to be effective compared to control group. Statistical analysis showed that significant difference was seen while assessing the efficiency of transdermal patch.

Graph 1 shows the mean of plasma concentration among the case and control group which clearly shows that plasma concentration was higher in case than the control group. Graph 2 shows the vas score in 2 hours among the case and control group which showed no change in both case and control group with neutral results. Graph 3,4,5 shows the vas score in 6 hours, 12 hours and 24 hours which showed that graphically pain was felt lower in case group than the control group. Graph 6 shows the mean of efficacy of transdermal patch for 24 hours among the case and control group which showed graphically case was effective than control group.

TABLE 1: DESCRIPTIVE STATISTICS OF PLASMA CONCENTRATION AMONG THE CASE AND CONTROL GROUP

VARIABLES	**CASE GROUP**	**CONTROL GROUP**
Mean	997.1758	851.5808
Std. Error of Mean	21.02417	12.37870
Std. Deviation	72.82985	42.88109
Variance	5304.187	1838.788
Range	204.40	149.50
Minimum	909.00	808.00
Maximum	1113.40	957.50

TABLE 2: COMPARISON OF MEAN DIFFERENCE OF PLASMA CONCENTRATION AMONG THE CASE AND CONTROL GROUP

STUDY GROUPS	**VARIABLES**					**t**	**df**	**P-value**
	Mean	**Std. Deviation**	**Std. Error Mean**	**95% Confidence Interval of the Difference**				
				Lower	Upper			

CASE VS CONTROL GROUP	145.59500	103.47243	29.86992	79.85175	211.33825	4.874	11	.001*

TABLE 3: DESCRIPTIVE STATISTICS OF VAS SCORE IN 2 HOUR AMONG THE CASE AND CONTROL GROUP

VARIABLES	**CASE GROUP**	**CONTROL GROUP**
Mean	1.4167	1.4167
Std. Error of Mean	.28758	.28758
Std. Deviation	.99620	.99620
Variance	.992	.992
Range	3.00	3.00
Minimum	.00	.00
Maximum	3.00	3.00

TABLE 4: COMPARISON OF MEAN DIFFERENCE OF VAS SCORE IN 2 HOUR AMONG THE CASE AND CONTROL GROUP

STUDY GROUPS	**VARIABLES**					**t**	**df**	**P-value**
	Mean	**Std. Deviation**	**Std. Error Mean**	**95% Confidence Interval of the Difference**				
				Lower	Upper			
CASE VS CONTROL GROUP	.00000	1.26491	.38139	-.84978	.84978	.000	11	1.000

TABLE 5: DESCRIPTIVE STATISTICS OF VAS SCORE IN 6 HOUR AMONG THE CASE AND CONTROL GROUP

VARIABLES	**CASE GROUP**	**CONTROL GROUP**
Mean	2.3333	3.5833

Std. Error of Mean	.39568	.35799
Std. Deviation	1.37069	1.24011
Variance	1.879	1.538
Range	5.00	4.00
Minimum	.00	2.00
Maximum	5.00	6.00

TABLE 6: COMPARISON OF MEAN DIFFERENCE OF VAS SCORE IN 6 HOUR AMONG THE CASE AND CONTROL GROUP

STUDY GROUPS	**VARIABLES**					**t**	**df**	**P-value**
	Mean	**Std. Deviation**	**Std. Error Mean**	**95% Confidence Interval of the Difference**				
				Lower	Upper			
CASE VS CONTROL GROUP	-1.25000	1.35680	.39167	-2.11207	-.38793	-3.191	11	.009*

TABLE 7: DESCRIPTIVE STATISTICS OF VAS SCORE IN 12 HOUR AMONG THE CASE AND CONTROL GROUP

VARIABLES	**CASE GROUP**	**CONTROL GROUP**
Mean	4.2500	5.0833
Std. Error of Mean	.32856	.31282
Std. Deviation	1.13818	1.08362
Variance	1.295	1.174
Range	4.00	3.00
Minimum	2.00	4.00

Maximum	6.00	7.00

TABLE 8: COMPARISON OF MEAN DIFFERENCE OF VAS SCORE IN 12 HOUR AMONG THE CASE AND CONTROL GROUP

STUDY GROUPS	**VARIABLES**					**t**	**df**	**P-value**
	Mean	**Std. Deviation**	**Std. Error Mean**	**95% Confidence Interval of the Difference**				
				Lower	Upper			
CASE VS CONTROL GROUP	-.83333	1.26730	.36584	-1.63854	-.02813	-2.278	11	.044*

TABLE 9: DESCRIPTIVE STATISTICS OF VAS SCORE IN 24 HOUR AMONG THE CASE AND CONTROL GROUP

VARIABLES	**CASE GROUP**	**CONTROL GROUP**
Mean	5.8333	6.9167
Std. Error of Mean	.38599	.39807
Std. Deviation	1.33712	1.37895
Variance	1.788	1.902
Range	4.00	4.00
Minimum	4.00	5.00
Maximum	8.00	9.00

TABLE 10: COMPARISON OF MEAN DIFFERENCE OF VAS SCORE IN 24 HOUR AMONG THE CASE AND CONTROL GROUP

STUDY GROUPS	**VARIABLES**				**t**	**df**	**P-value**
	Mean	**Std. Deviation**	**Std. Error Mean**	**95% Confidence Interval of the Difference**			

				Lower	Upper			
CASE VS CONTROL GROUP	-1.08333	1.31137	.37856	-1.91654	-.25013	-2.862	11	.015*

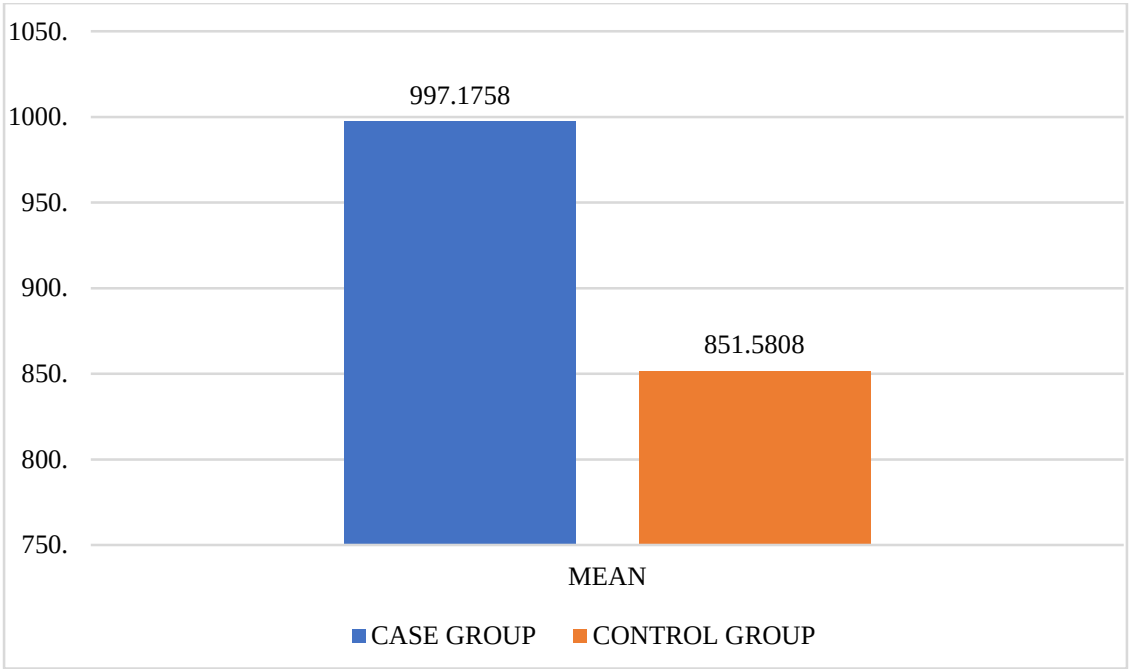
TABLE 11: DESCRIPTIVE STATISTICS OF EFFICACY OF TRANSDERMAL PATCH FOR 24 HOURS AMONG THE CASE AND CONTROL GROUP

VARIABLES	**CASE GROUP**	**CONTROL GROUP**
Mean	15.8333	12.4167
Std. Error of Mean	1.18599	1.43790
Std. Deviation	4.10838	4.98102
Variance	16.879	24.811
Range	16.00	16.00
Minimum	8.00	6.00
Maximum	24.00	22.00

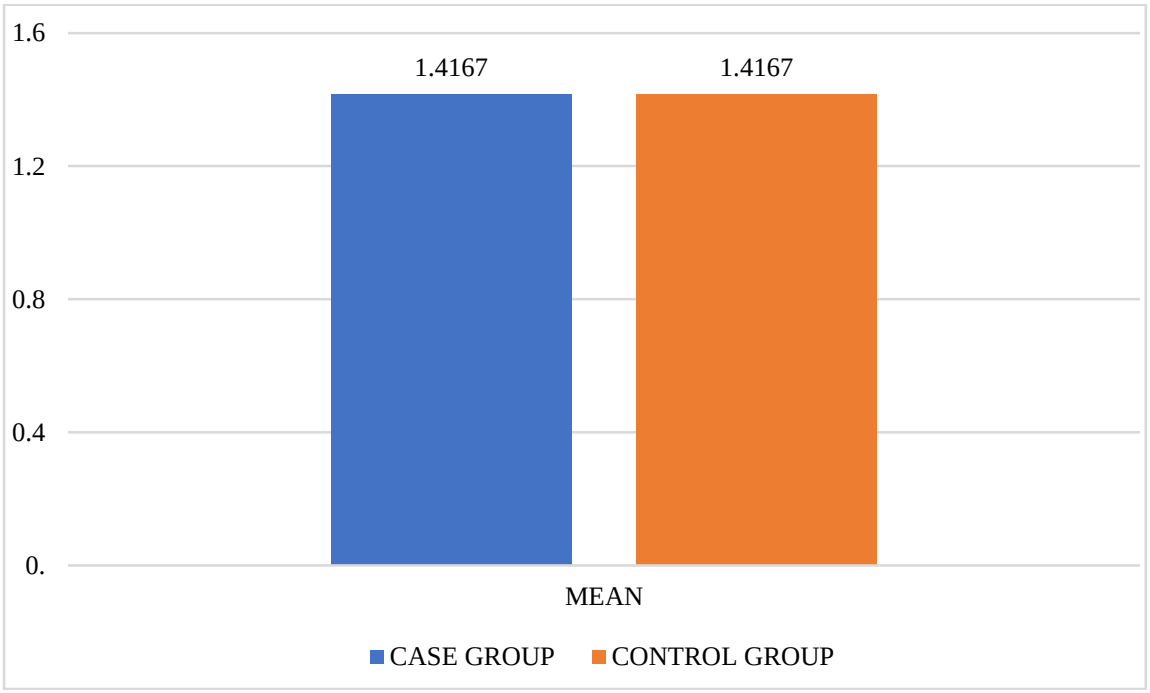
TABLE 12: COMPARISON OF MEAN DIFFERENCE OF EFFICACY OF TRANSDERMAL PATCH FOR 24 HOURS AMONG THE CASE AND CONTROL GROUP

STUDY GROUPS	**VARIABLES**					**t**	**df**	**P-value**
	Mean	**Std. Deviation**	**Std. Error Mean**	**95% Confidence Interval of the Difference**				
				Lower	Upper			
CASE VS CONTROL GROUP	3.41667	5.35059	1.54458	.01707	6.81627	2.212	11	.049*

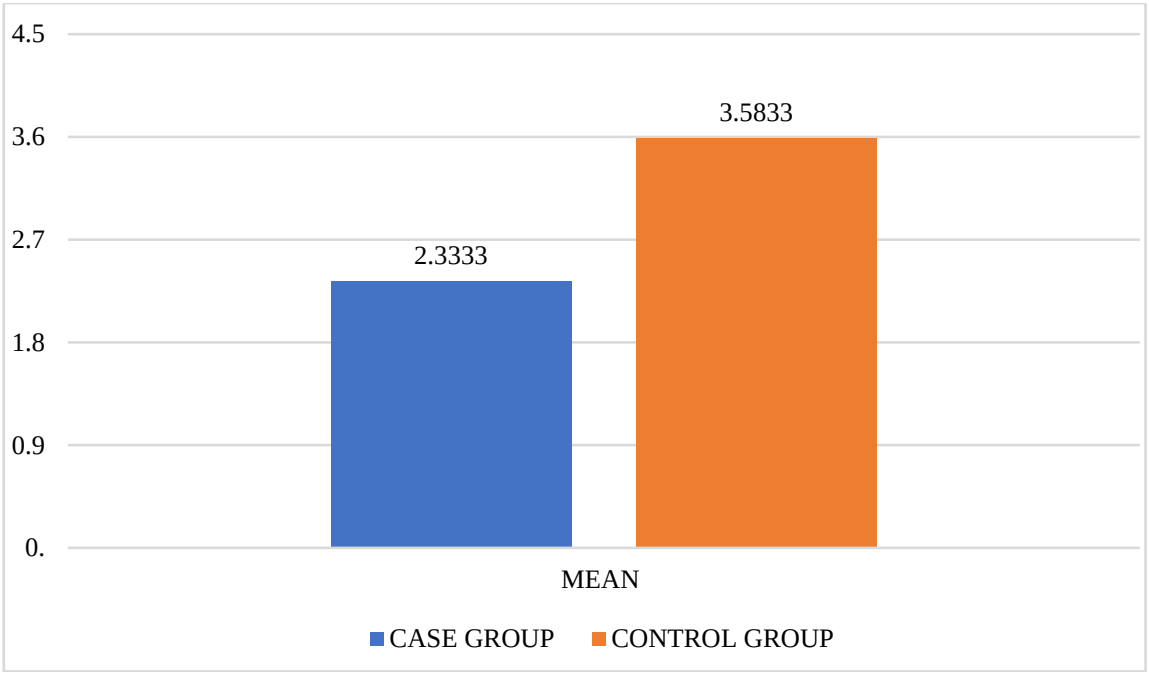
GRAPH 1: MEAN OF PLASMA CONCENTRATION AMONG THE CASE AND CONTROL GROUP



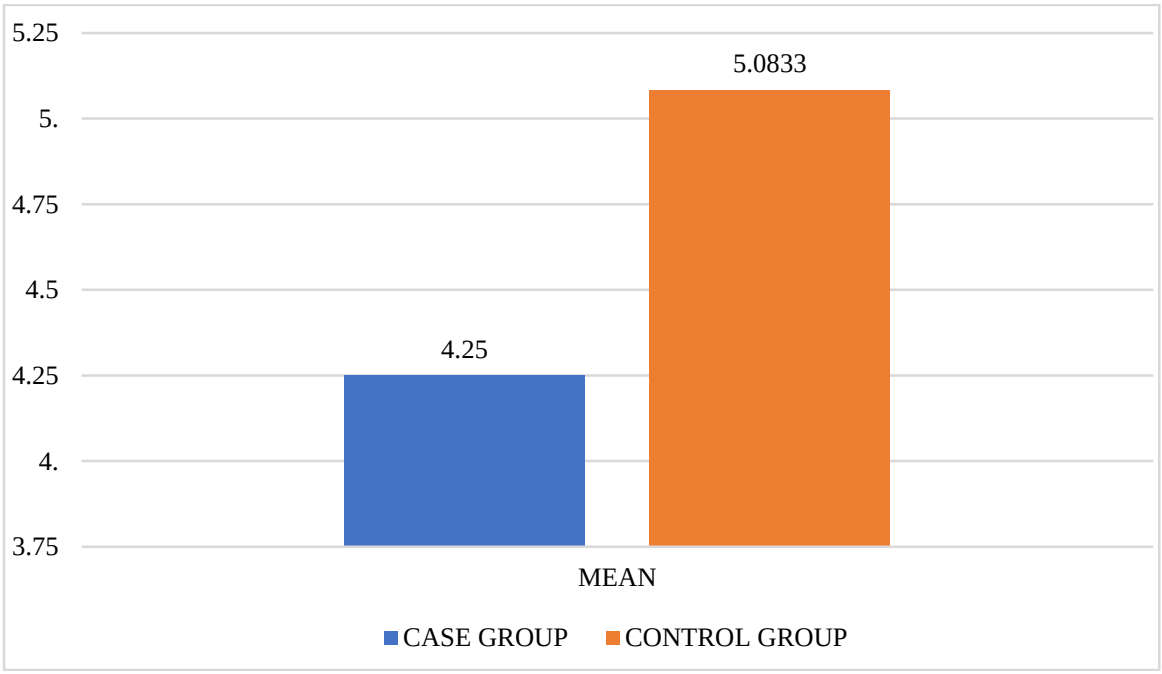
GRAPH 2: MEAN OF VAS SCORE OF 2 HOUR AMONG THE CASE AND CONTROL GROUP



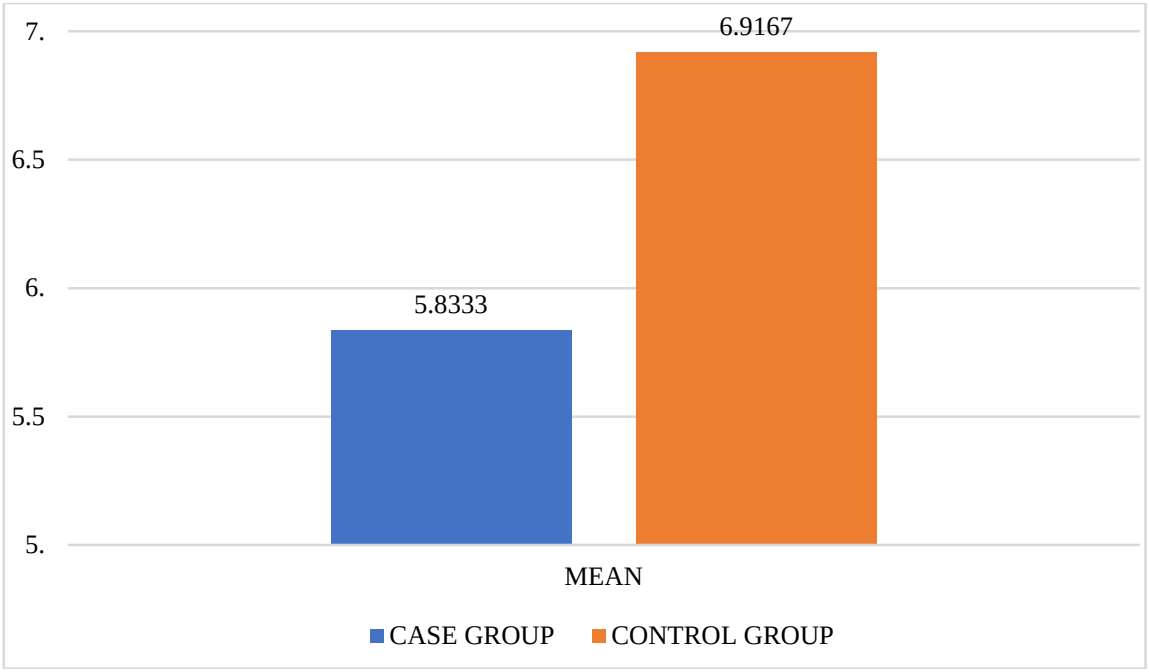
GRAPH 3: MEAN OF VAS SCORE OF 6 HOUR AMONG THE CASE AND CONTROL GROUP



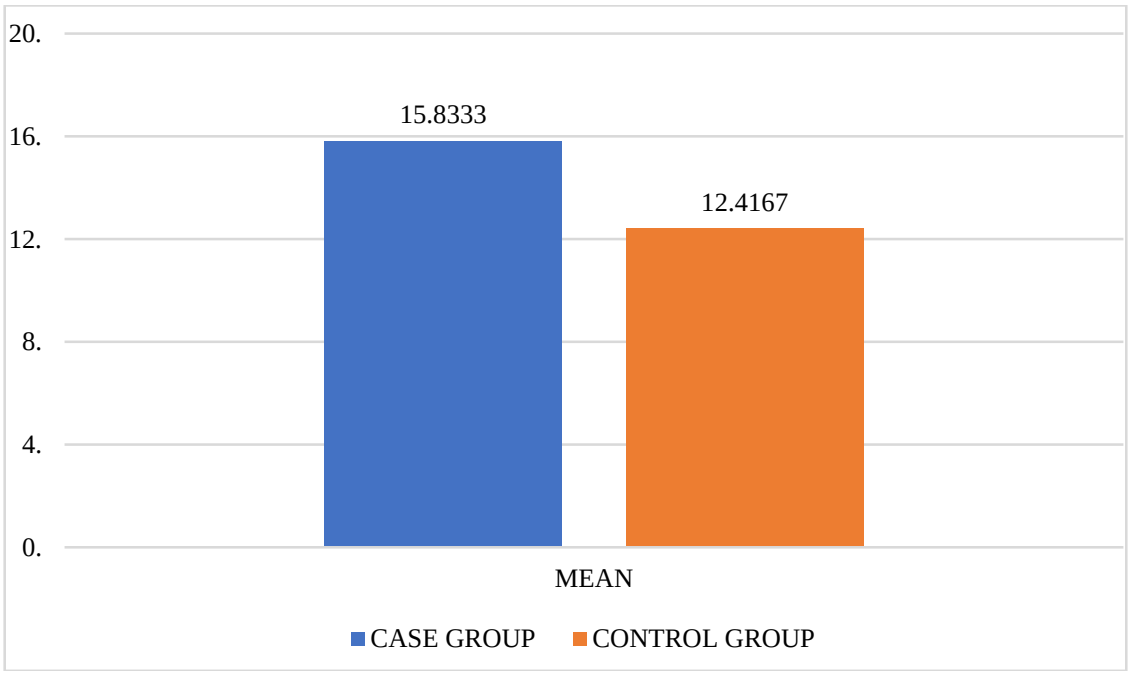
GRAPH 4: MEAN OF VAS SCORE OF 12 HOUR AMONG THE CASE AND CONTROL GROUP



GRAPH 5: MEAN OF VAS SCORE OF 24 HOUR AMONG THE CASE AND CONTROL GROUP



GRAPH 6: MEAN OF EFFICACY OF TRANSDERMAL PATCH FOR 24 HOURS AMONG THE CASE AND CONTROL GROUP



4. Discussion Manuscript Ongoing

Pain and Oral Surgery

Pain is an unpleasant sensation and emotional experience. Post operative pain is the most common outcome following maxillofacial surgery, which is unavoidable. Effective analgesia not only relieves the patient from the pain, but also improves the quality of life. Tissue damage following surgery evoke signals which tends to sensitize the peripheral and central pain pathways leading to initiation of pain. Postoperative pain is pain that occurs after a surgical procedure. It is a common problem experienced by patients undergoing surgery and can have a range of effects on the body, both physically and mentally. Physically, postoperative pain can cause a variety of symptoms such as increased heart rate, elevated

blood pressure, shallow breathing, muscle tension, decreased mobility, and reduced ability to perform daily activities. Pain can also lead to reduced appetite and sleep disturbance, which can further affect the body's ability to heal and recover from the surgery.

In addition to physical symptoms, postoperative pain can also have psychological effects, such as anxiety, depression, and decreased quality of life. Chronic pain, which can persist after the surgical wound has healed, can also lead to long-term changes in the nervous system and cause ongoing physical and psychological symptoms. Effective pain management is therefore important to ensure patients can recover well from surgery and return to their daily lives.

Pain creates a traumatic experience, where patients acceptance and motivation towards further and future treatments get affected.

The management of postoperative pain[28] is a crucial aspect of patient care following orthognathic surgery. modalities of pain management that can be used to alleviate pain and discomfort in patients undergoing orthognathic surgery.

One of the primary modalities of pain management is the use of pharmacological agents such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen. While opioids are effective in managing severe pain, their use is associated with side effects such as nausea, vomiting, and constipation.

Pre-emptive analgesia, is a potential mechanism (protective) ,where analgesic medications are administered prior to the surgery, which is known to be more effective than the treatment initiated after surgery[15]. Cyclooxygenase-2 inhibitors have been known to be used in pre-emptive analgesia in reducing post operative pain and also reduce the overall use of opioid as "opioids are associated with various treatment-limiting side effects and also their potential for dependence, Prolonged or even short-term exposure to opioids may put certain patients at risk for opioid use disorder[14], which has become a major public health crisis , that the healthcare system is increasingly cognizant of reducing the exposure of patients to prescription opioids for multiple reasons".

"Diclofenac {2-[(2,6-dichlorophenyl) amino] phenylacetate}" belongs to the group phenylacetic acid derivative a nonsteroidal anti-inflammatory drug (NSAID) and is a potent inhibitor of prostaglandin synthesis that shows preferential inhibition of the cyclooxygenase-2 (COX-2) enzyme[18]. "Its potent analgesic effects is used clinically for the short-term alleviation of post-operative pain." Other routes of administration being topical, intravenous, intramuscular, trans dermal, intra-coelomical, and rectal.

Oral route of administration of a drug undergoes first pass metabolism i.e., drugs must first pass from the intestine(GI) to the liver (Hepatic) before reaching the general circulation. Reduced drug concentration before reaching the tissues as they are metabolized by gut flora or digestive enzymes, the combined effective metabolism by the liver and gut is referred as First pass metabolism. But as studies suggest that the food intake delays the absorption of enteric coated tablets due to an increasing of gastric emptying time and small intestinal transmit time.

(Upper &Lower) gastrointestinal complications have been reported with the use of DICLOFENAC that includes "*reflux, belching, bloating and /or nausea*" by inhibiting the production of protective mucus in the stomach. The recorded cases of lower GI injury associated with NSAID use is somewhat lower than that of upper GI injury, and when coadministered with the oral corticosteroids there was as increased incidence in the rate of GI complications as much as two-fold[19].

In the transdermal drug delivery systems, the skin us used as the site of drug administration where it gets absorbed into the systemic circulation through the blood capillaries present in the dermis layer of skin and not only helps to overcome the first pass metabolism of the oral and injectable forms but is also a patient friendly alternative[22]. In the fifteenth century, "Primary transdermal formulations found to be was Unguent Hydrargyria, formulation containing mercury for treatment of syphilis". German pharmacist, Paul Carl Beiersdorf in 1880 developed a (plaster-based) formulation to treat skin disorders. Emplastrum belladonna made of atropabelaldona is one of the well-known plasters for the treatment of tuberculosis and tumor[21].

Scopolamine (Transderm Scop®, 1979) was (1st transdermal) marketed for the treatment of motion sickness had reduced side effects when compared to oral administration. Studies (research) have revealed that Hepatic first pass metabolism can be bypassed and a steady state plasma concentration of the drug over a extended time can be maintained. The advantages of transdermal patches over oral administration include. Reduction in the frequency, non-invasiveness, ease of application and termination resulting in the improved patient compliance.

Transdermal diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that can be used for postoperative pain management. This medication is applied as a patch that is placed on the skin, allowing for slow and steady release of

the drug over time. Studies have shown that transdermal diclofenac can be effective for postoperative pain management, particularly in patients undergoing certain types of surgery such as orthopedic surgery. It has also been shown to have a lower risk of gastrointestinal side effects compared to oral NSAIDs.

First-pass metabolism refers to the process of drug metabolism that occurs in the liver and intestines after oral administration of a drug. The liver and intestines contain enzymes that can metabolize drugs, and this process can significantly alter the concentration of the drug that reaches the systemic circulation. After oral administration, the drug is absorbed through the intestines and then passes through the liver via the portal vein before it enters the systemic circulation. During this process, the drug is exposed to enzymes in the liver and intestines that can break it down, resulting in a lower concentration of the drug in the systemic circulation. The effect of first-pass metabolism on drug concentration in the systemic circulation can be significant. For some drugs, first-pass metabolism can result in a significant reduction in the amount of the drug that reaches its intended target. In some cases, this can limit the effectiveness of the drug or require a higher dose to achieve the desired therapeutic effect.

During first pass metabolism of diclofenac, it is metabolized by several hepatic enzymes, including cytochrome P450 (CYP) enzymes, glucuronyl transferases, and sulfotransferases. These enzymes convert diclofenac into several metabolites, including 4'-hydroxydiclofenac, 5-hydroxydiclofenac, and 3'-hydroxydiclofenac. The major metabolite of diclofenac is 4'-hydroxydiclofenac, which has similar pharmacological properties to the parent drug. However, the metabolites of diclofenac are less potent than the parent drug, and their contribution to the overall therapeutic effect is limited.

Due to first pass metabolism, the bioavailability of orally administered diclofenac is relatively low, ranging from 50 to 60%. This means that only a portion of the drug that is ingested reaches the systemic circulation and is available for its intended therapeutic effect. To circumvent the first pass metabolism of diclofenac, alternative routes of administration have been developed, including transdermal, topical, and rectal administration. These routes of administration can bypass the liver and deliver the drug directly to the systemic circulation, increasing the bioavailability and efficacy of the drug.

To overcome the limitations of first-pass metabolism, some drugs can be administered via non-oral routes, such as intravenous or transdermal administration. This can help to bypass the liver and intestines, resulting in a higher concentration of the drug in the systemic circulation. Diclofenac diethylamine is a topical formulation of diclofenac, which is used for the treatment of localized pain and inflammation. It contains diclofenac, a nonsteroidal anti-inflammatory drug (NSAID), in the form of diclofenac diethylamine salt, which is a water-soluble salt that is easily absorbed through the skin.

Diclofenac diethylamine is a water-soluble salt that is designed to enhance the transdermal absorption of diclofenac. When applied topically, it is absorbed through the skin and enters the systemic circulation, providing localized pain relief without the potential side effects associated with oral administration. Diclofenac diethylamine is primarily used as a topical medication for the management of localized pain, particularly in musculoskeletal conditions such as osteoarthritis and rheumatoid arthritis. However, it is also used for systemic pain relief in some instances. When used for systemic pain relief, diclofenac diethylamine is typically administered as a patch, which delivers a consistent dose of the medication over a period of time. The patch is applied to the skin and absorbs into the bloodstream, providing pain relief throughout the body.

One of the main advantages of transdermal drug delivery is that it provides a non-invasive method of drug administration. This can be particularly beneficial for patients who have difficulty swallowing or who require frequent dosing. Transdermal patches can be easily applied to the skin and do not require any needles or other invasive procedures. Another benefit of transdermal drug delivery is that it provides a controlled and consistent drug release over an extended period of time. This can help to maintain a steady level of medication in the bloodstream and avoid peaks and troughs associated with oral administration. This can be especially important for medications that require continuous or long-term treatment

Skin acts as the main site of absorption for many drugs for both topical and transdermal routes. It is divided into two layers the outermost layer epidermis which is approximately 50-100 µm consisting of 5 different layers. The most superficial layer known as **Stratum corneum** (SC) comprising of 15-30 layers of corneocyte cells makes upto a thickness of 10-20 µm, and components like “dead keratinocytes” together with “ceramide lipid” component forms a compact

assembly known as (brick-and-mortar) arrangement. Molecular structure termed as Corneodesmosomes formed by keratinocytes which are inter -connected by glycoprotein desmosomes, where drugs need to first permeate to get absorbed into skin and then into circulation. This complex arrangement prevents the drugs from penetrating and getting absorbed, functioning as barrier mechanism of skin. Beneath this layer is the **stratum lucidum, stratum granulosum, stratum spinosum and at last the stratum basale** and the innermost layer dermis which is further divided into "Papillary and Reticular" layers where the blood vessels along with the lymphatic capillaries exist[21].

In general drug absorption from the SC is divided into **Trans-appendageal**, drug delivery through hair follicles and sweat glands and is useful in transportation of large macromolecules and also polar and compounds that are ionisable which cannot pass through transepidermal pathway. Being the main route of absorption **Transepidermal** where drug from the transdermal patch spread onto skin and permeate either through transcellular or intercellular routes. Because of hydrophobic nature lipid complexes in the cell membranes of SC, the hydrophobic drugs permeate through transcellular route and hydrophilic and small molecules diffuse through lipid matrix. Drug molecules which are sufficiently lipid and aqueous soluble are dependent on the dominant intercellular route for drug absorption, to finally reach vascular capillaries in the dermis.

Factors such as "Skin physiology, thickness of (stratum cornem), amount of lipid in different parts of the skin layers" influence absorption rate of drugs into the skin. Quantity of capillary blood vessels in certain skin body parts may have an impact on the rate of drug absorption into the circulation. To overcome the limitations or challenges caused by the stratum corneum, the researchers have come up with several methods in enhancing drug absorption by modification of structure of SC, either physically, chemically or using combination of both. Drug – vehicle interaction and vesicles and analogues, stratum corneum modification are the different strategies (approaches) used to deliver the drugs transdermally[23].

Transdermal drug delivery has evolved over the years into first, second and third generations depending on the mode of delivery being employed (Prausnitz and Langer). Second generational delivery systems delivered drug by

A.Drug-prodrug
B.Ion pairing
C.Eutectic systems
D.Chemical potential or thermodynamic methods

which aimed at increasing the skin permeability by modifying the SC and providing an additional driving force / pressure across the skin.

Drug permeation into the skin can be improved by "modification" of the structural properties of SC without damaging the skin, by hydration and chemical enhancers as given by Morrow et.al.,. Chemicals used have to be non-toxic, non-allergenic, inert and non-irritant, and show rapid effects and most importantly the function of the barrier must recover as soon as possible. They are classified based on the properties of chemicals and mechanism of action into 1) sulphoxides 2) azones , 3) pyrrolidone, 4) fatty acids, 5) Alcohols, 6)surfactant 7)urea , 8)Terpenes .

Dimethyl sulfoxide (DMSO) interacts with the lipid domains of SC and may also change the intercellular keratin conformation by denaturing the protein components. And by altering the diffusivity enhances the transdermal delivery of hydrophilic drugs. Using DMSO as permeation enhancer, several drugs such as fentanyl hydrobromide, naloxone, testosterone and hydrocortisone were delivered transdermally.

Coming to the pharmacokinetic properties of the transdermal drug delivery, the energy to diffuse the drug through the patch comes from high concentration gradients present within the patch as a saturated solution of drug in the system s compared to the lower concentrations in the skin. The rate of permeation can be calculated using "dm/dt=DCoP/h"

where

-D is the diffusion coefficient-

- Co the constant concentration of drug in the patch-
- P the partition coefficient between the skin and bathing solution-
- h the thickness of the skin-

- **DIFFERENT TYPES OF TRANSDERMAL PATCHES CURRENTLY AVAILABLE ARE**:
- 1. Single-layer drug-in-adhesive patch
- 2. Multi-layer drug-in-adhesive
- 3. Reservoir patch
- 4. Matrix patch

To sustain the release characteristics of Diclofenac Diethylamine, it must be formulated into matrix type patches. In combating mild to moderate post-operative pain following impacted 3rd molar removal, with its proven analgesic effectiveness, better patient compliance, reduced side effects transdermal diclofenac has shown promising results and acts as exceptional alternative in "oral and parenteral" drug administration, capable of employing in post-surgical and post traumatic pain.

In addition to its benefits, transdermal drug delivery also has some limitations. Not all drugs can be delivered through the skin, as the skin acts as a barrier that can prevent certain drugs from being absorbed. Additionally, some drugs may require high doses to be effective, which may not be possible to achieve through transdermal delivery.

Furthermore, some individuals may experience skin irritation or allergic reactions to the adhesive used in transdermal patches, which can limit their use. Additionally, transdermal patches must be replaced regularly, which can be a disadvantage for patients who may forget to change the patch or who have difficulty adhering to a strict medication regimen. One of the key advantages of transdermal drug delivery is its ability to bypass the gastrointestinal tract, which can lead to a reduced risk of gastrointestinal side effects such as nausea and vomiting. In addition, it can also bypass the liver, which can metabolize drugs and reduce their effectiveness.

With high affinity and great capacity at therapeutic concentration, diclofenac is expansively/ extensively (>99.7%) bounds with plasma and serum and in solution of human serum albumin. The diclofenac bound to plasma can be determined by using measurement of absorbane of the solutions at a fixed wavelength and by using a multi-wavelength computational program in procesing the spectrophotometric data within a selected range, “analysis is performed measuring the peak-to-peak amplitude”in the first derivative UV spectrum using UV Spectrophotometry.

SUMMARY

Pain is an unavoidable outcome of maxillofacial surgery, affects the recovery period of the patient in the immediate post-op period. Management of pain with minimal systemic side effects using NSAIDS (Diclofenac Diethylamine – NUPATCH 200mg) can be achieved by transdermal route of drug administration, which has its own limitations such as reduced permeation because of the natural barrier mechansm of skin (stratum corneum). Of all the methods available to enhance the drug permeation-chemical permeation enhancers (Dimethyl sulfoxide) is used to increase the plasma drug concentrations. This helps in better pain management and ease the patients stay in the hospital and improve the quality of life.

5. Conclusion

Transdermal drug delivery avoids the complications related with traditional pain management strategies available currently. As every mechanism has its limitations, hindrance in absorption of drug from the transdermal patch by the stratum corneum of skin due to its (barrier) protective mechanism is vital. This can be altered for a limited period without causing permanent damage with the help of a chemical permeation enhancer (Dimethyl sulfoxide) as an adjuvant, one of the modalities available. UV spectroscopy studies revealed increased plasma concentrations of drugs (NSAIDS-DICLOFENAC DIETHYLAMINE) for longer duration which facilitate better management of pain helping the patient recover when compared to patients either on transdermal patches alone, oral or I.V drug administration.

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