MUCOADHESIVE PATCHES OF PREGABALIN EFFECTIVE IN THE TREATMENT OF NEUROPATHIC PAIN: A SYSTEMATIC REVIEW

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ABSTRACT

Although the oral pathway is the recommended mode of intake for the majority of medications, it does have some drawbacks i.e., pre-systemic metabolism in the liver, gastrointestinal disturbance, and enzyme degradation. It offers a safe method for administration of medications and easy way to reverse the intake of toxic substances by easy removal of dosage form from oral cavity. This review was designed to critically acknowledge the evaluation parameters, mechanism of cohesion, polymers used in mucoadhesive formulation, main method of preparations (solvent casting & milling), advantages & disadvantages of mucoadhesive patches. This review consists an extensive survey of literature from the Scopus, PubMed, Springer Nature and other international reputed sources. Since the middle of 1980s, the idea of muco-adhesion has acquired extensive interest in drug innovation. Muco-adhesive dosage structures were developed for oral delivery like adhesive unit dosage form, adhesive gels and adhesive patches. The epithelium that forms the internal lining of buccal mucosa is the primary obstruction for the drugs absorption. Muco-adhesion is defined as an interfacial adhesion in which one synthetic mucoadhesive polymer and the other mucin layer (mucosal tissue), are hold together by an attraction force. 'Mucoadhesive' is defined as an artificial substance being capable of making interaction with mucus membranes and binding them together for extended or delayed periods of time. However, delivering therapeutically for the therapy of both systemic and topical disorders would take a lot more work with these innovative mucoadhesive formulations. In conclusion, it facilitates the target therapy by enriching efficacy or intrinsic activity.

Keywords: *mucoadhesive patch, solvent-casting, milling, mechanism of muco-adhesion, polymers*

Introduction

Although the oral pathway is the recommended mode of intake for the majority of medications, it does have some drawbacks i.e., pre-systemic metabolism in the liver, gastrointestinal disturbance, and enzyme degradation. To overcome such problems, a route came in knowledge that includes several as intranasal, buccal, transdermal and pulmonary routes that deliver the drugs in systemic circulation and bypass the pre-systemic metabolism [1]. Use of mucoadhesive polymers can significantly enhance the residence period (on mucosa) of the dosage form [2]. It offers a safe method for administration of medications and easy way to reverse the intake of toxic substances by easy removal of dosage form from oral cavity [3]. Advancement of new drug molecule is costly and tedious. Further developing well-being viability ratio of "old" drugs endeavored utilizing numerous strategies i.e., individual drug treatment, dose titration, and therapeutic drug monitoring [4]. Mucoadhesion has sparked a lot of interest in medication development since the middle of the 1980s [5].

The transformation of a current medicine molecule from a normal structure to a unique delivery method can have a significant impact on its display in terms of silent consistency, security, and adequacy [6]. In comparison to the oral pathway of drug delivery, buccal delivery is one of the choices, especially for treatments that go through first pass effect. permeation of water - soluble medication through the film serves as one of the main limiting factors in the development of bio-adhesive buccal delivery devices [7]. This approach provides a number of advantages, such as avoidance of discomfort, tissue injury, pre-system metabolism, and a decrease in hepatic side effects, which are frequent when utilizing the parenteral route. The polymers used to deliver drugs *via* rectum, vaginal cavities include gelatin, polycarbophil, mucin and poloxamers [8]. Mucoadhesive patches are becoming an essential tool having optimum delivery of medicines with rapid and maximum bioavailability. It is highly recommended to administer the drugs as mucoadhesive patches that deliver systemic effects.

Oral Mucosal Delivery Pathway

Oral mucosal delivery is divided into 3 types as below-

a. Buccal
b. Sublingual
c. Local

a. Buccal delivery

In comparison to the oral pathway of drug administration, buccal delivery of pharmaceuticals is one of the choices, especially for drugs that go through pre-systemic metabolism. Adhesive mucosal dosage structures, including as adhesive unit dosage forms, gels, and patches have been created for buccal pathway of delivery. The epithelium (forming internal linings) acts as primary barrier for absorption of drugs.

Facilitated penetration of the medication through the mucus buccal layer and diminishing of degradation of drugs by enzymes is achieved by doing some physicochemical modifications. Permeability through buccal mucosa is increased by the using permeation enhancer [7].

b. Sublingual delivery

Sublingual medication delivery is viewed as a promising route for quicker and direct ingestion of medication into blood stream. In buccal cavity, sublingual region is generally penetrable for drug ingestion. The part of medication consumed through the sublingual veins sidesteps the pre-systemic digestion, which prompts more prominent BA and better patient compliance. New sublingual improvements meet a variety of drug and patient needs, from improved life-cycle control to beneficial dosing for dysphagic paediatric, geriatric, and mental patients [9].

c. Local delivery

The local drug delivery system has the potential of controlled release properties that provides an actual but limited and beneficial response specially on periodontal pockets [10]. Through various interaction mechanisms, the mucoadhesive preparation can make adherence to the mucosal film and boost the retention and diffusion power of bioactive combinations. Because this pathway avoids pre-systemic digestion and travels through the gastrointestinal system, absorption of bioactive mixtures from mucosa can facilitate bioavailability [11].

Mechanism of Muco-Adhesive

Muco-adhesion is defined as an interfacial adhesion in which one synthetic mucoadhesive polymer and the other mucin layer (mucosal tissue), are hold together by an attraction force. [12]. . 'Mucoadhesive' is defined as an artificial substance being capable of making interaction with mucus membranes and binding them together for extended or delayed periods of time [8].

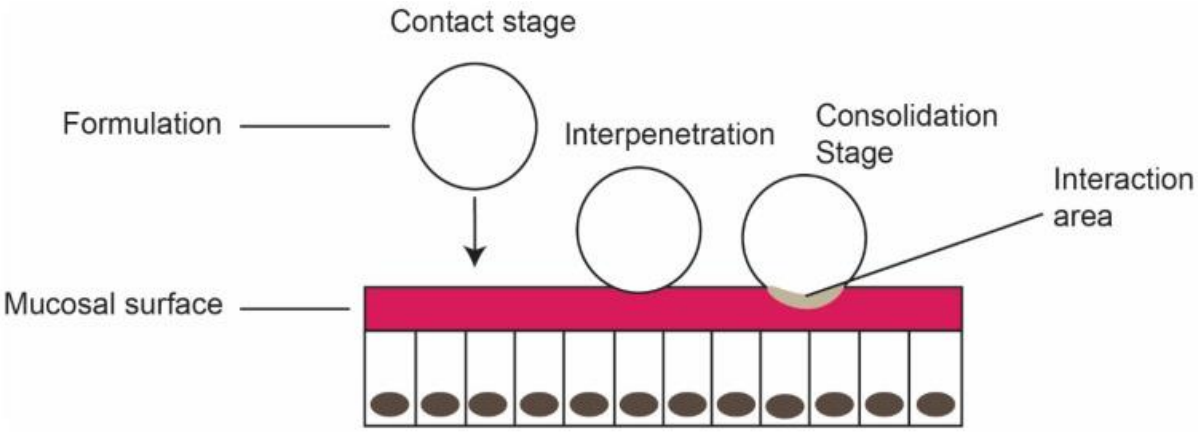

Fig 1. Stages of mucoadhesion

There are two stages evolved in the adhesion process as follows-

1. Contact stage

In this stage, when the mucoadhesive substance interacts with mucus membrane, Between the mucoadhesive and the mucous film, there is an initial wetting. The mucus present in the mucosal film completes the wetting of the mucoadhesive.

Consolidation stage

Mucoadhesive substance adheres to a mucus layer due to the attraction of biophysical forces, resulting in long-lasting muco-adhesion. The consolidation stage is what it's called [13].

Methods of Preparations

These following mentioned methods are most frequently used for the development of mucoadhesive patches-

1. Solvent casting method

This method involves the co-dispersion of excipients along with the drug in solvent (organic) and coated on polymer release sheet. A laminate is made by laminating a thin layer of protective backing substance on coated polymer release sheet. At last, it is cut-down to isolate patches of the preferred size & design [14].

2. Milling method

Direct milling method is utilized for mechanized blending of drug with excipients without involving any condensed matter. By sliding the notable material, the desired thickness can be refined. After that, the backing substance is covered. Solvent-free environment is chosen since there is no risk of residual solvents/ health risks that solvents can trigger [15].

Characterization Methods of Mucoadhesive Patches

1. Weight variation

The all the buccal patches will be determined for their weights and to compare among to make sure that these are under limits of weight variation.

2. Flatness

Both sides will assess the flatness of each patch. Both sides will assess the flatness of each patch. The length of every stripe is measured, as is the variation in length, because consistency in flatness indicates tightness, with 0% constriction equaling 100% flatness.

3. Endurance

Folding endurance is assessed by folding one patch until it split-down. It also checked by folding it about 250 times without damaging it. The no. of times of patch twisted with the same place without breaking is used to estimate folding durability [16].

4. Moisture loss

Mucoadhesive patches are separately weight and placed in Desiccator with calcium chloride (anhydrous). After, same patches are removed and weighed after 3 days for moisture loss (%) [17]. The formula was used to compute the % absorption of moisture and moisture loss:

$$\text{Percentage moisture absorbed} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \text{ X } 100$$

5. Drug content determination

A little section of the patch is sliced and solubilized in PBS solution (pH 7.4). To increase the solubility, ethanol is added, the remaining volume is diluted to 100 ml with PBS (pH 7.4). The solution is then drained of 1 ml and diluted to a final concentration of 10 ml. The solution's absorbance is measured at 270 nm, and the concentration is determined. As a result, the drug content is determined [18].

6. Surface pH measurement

Backing layer less Patches are allowed to absorb the content for 3 hours on an agar plate consisting 2% m/v agar in synthesized human saliva (pH 6.8). Continuously stirred, then transferred into a Petri-dish and allowed to solidify at 25±2ºC. The pH of the surface of swollen patch is tested with a litmus paper placed on top of it [19, 20].

7. Drug release from backing layer

The Franz-Diffusion Cell is incorporated in determination of drug release from the backing layer. A bi-layered patch is kept b/w the donor & receptor compartments. The entire unit is kept at 37°C with synchronous stirring, and the donor compartment is filled with synthesized human saliva (3ml) pH 6.8 and in receptor compartment, phosphate buffer (21ml) added pH 7.4. Each time, 2ml of sample is taken from donor compartment at specified intervals and evaluated by UV spectrophotometric analysis at 205 nm to assess drug release from the patch [21].

8. Drug content uniformity

Patches with a diameter of 25mm and a content of 55mg of LP were homogenized for 5 hours with periodic shaking in a mixture of ethane (5ml) and dichloromethane (2ml), and diluted with 50ml purified water. 1ml of filtrate is dissolved in 10ml synthesized human saliva (pH 6.8) after filtration to eliminate insoluble residue. An ultraviolet (UV) spectrophotometer is used to measure the absorbance at 205nm. Every patch formulation, the tests are done in triplicate [22].

9. Drug release study (*in-vitro)*

In a dissolution test device, drug release from the patches is studied. Synthesized human salva (250ml) served as dissolve medium at 37°C (pH 6.8) and continuously stirred with 50 rpm. Cyanoacrylate adhesive is used to adhere a patch of 2.5cm (in width) on a glass disc. The disc (containing patch at upper end) is placed at the bottom of dissolution tank. At the interval of 30 minutes, 5 ml of sample is withdrawn and replaced with 5ml of dissolving media. The sample is filtered-off thru 0.45mm filter paper and diluted in synthesized human saliva (pH 6.8) before being measured at 205nm using spectrophotometer. The experiment is repeated three times to minimize the errors [23][24].

10. Tensile strength

Force of attraction polymer complexes is evaluated using plastic (Poly Vinyl Chloride) sheet. The polymer and plastic plates are trimmed up to 1cm2 with thickness 0.8mm. The polymer is prewetted with water before being put on plastic plate. Before the measurement, they are held in contact with plastic plate for 2 minutes with the force of a "finger-tip." It was determined how much force is needed to separate the polymer from plastic plate [25].

11. Swelling index

Three patches are pre-weighed of 10mm diameter and placed in Petri-dish to determine the swelling index (containing 20 ml of water). The patches were removed after 5, 10, and up to 30 minutes, and the extra water on surface is cleaned through filter-paper. The enlarged areas were precisely measured for weight [26].

The % of swelling index is calculated by below mentioned formulae-

$$\text{Swelling Index} = \frac{W2 - W1}{W1} \times 100$$

Polymers- Category Used in Mucoadhesive Formulations

This table denotes compounds/ polymers used in the development of mucoadhesive patches for specific actions [27] as per their mechanism of action (Table 1.).

Advantages of Mucoadhesive Patches [5, 28, 29, 30, 31]

Mucoadhesive patches offer a few benefits over other buccal drug delivery systems by uprightness of increasing residence time of medication in g.i.t.-

1. Selective measurement structure of a particular segment.
2. It gives a highly rich vascularized medium of drug ingestion.
3. Avoid first pass metabolism thus subside its destruction in the g.i.t.
4. This is patient convenient pathway of drug ingestion in other non-oral routes.
5. Additionally, mucoadhesive patches give personal link b/w dose structure and absorption mucosa, bringing about high permeability.
6. In case of unconscious or uncooperative patients, mucoadhesive drug delivery is a simple solution.
7. Drugs with low oral bioavailability can have their bioavailability improved by including mucoadhesive delivery systems into their formulation.
8. High patient acceptance is seen in buccal medication delivery as it has a relatively quick onset on action in contrast to other methods- non-oral.

Disadvantages of Mucoadhesive Patches [28]

1. It demonstrates decreased permeability at buccal layer in comparison with sublingual layer.
2. This pathway has less surface-area .
3. Continuous secretion of saliva decreases the concentration of the drug/ dosage form.
4. Intake of saliva may cause decrease in its total dose.

Features of an Ideal Mucoadhesive System [32]

The following properties are considered in ideal mucoadhesive system-

1. Quick adherence ability to buccal layer
2. Sustained drug release
3. Increased bioavailability
4. High patient acceptance
5. Free from disturbing normal activities i.e. eating
6. Free from exhibiting dental decay (caries)
7. Broad safety index (local, systemic)

Mucoadhesive polymers are important for extending the residence period of dosage forms in the buccal cavity, which is accomplished thanks to the polymer's hydrophilic characteristics. Salient features of polymers [33][34] are considered as below-

- Amino-, carboxyl, hydroxyl and sulphate groups are strong hydrogen bonding groups
- Functional groups (strongly anionic or cationic)
- Large molecular weight
- Surface tension that encourages mucus layer spreading
- Flexible supply chain
- Loading capacity for bioactive substances
- Swell after hydration
- Interact with mucus
- Bioactive to be released in a controlled manner
- It ought to be biodegradable

Neuropathic pain

Pain induced by a somatosensory system injury or disease is a widely recognised definition. Touch, pressure, pain, temperature, position, movement, and vibration are all sensed by the somatosensory system. The somatosensory nerves are widely found in skin, muscles & fascial muscles, joints that comprise thermoreceptors, mechanoreceptors, chemoreceptors, pruriceptors, and nociceptors are that send signals to the spinal cord and eventually to the brain for further processing (BOX 1); most sensory processes involve a thalamic nucleus receiving a sensory signal and then directing it Postherpetic neuralgia, trigeminal neuralgia, painful radiculopathy, leprosy, HIV infection and diabetic neuropathy are common conditions associated with neuropathic pain; lesions or diseases of the somatosensory nervous system can lead to altered and disordered transmission of sensory signals into the spinal cord and brain [36].

Epidemiology

The incidence and prevalence of neuropathic pain in the global population are challenging to assess due to a lack of agreement on what constitutes neuropathic pain. In a systematic review of the epidemiology of chronic pain, a prevalence of 3% to 17% was discovered, with

incidences of 3.9–42.0/100,000 person-years for post-herpetic neuralgia, 12.6–28.9/100,000 person-years for trigeminal neuralgia, 15.3–72.3/100,000 person-years for PDN, and 0.2–0.4/100,000 person-years for glossopharyngeal neuralgia. Furthermore, neuropathic pain was more common in women (60.5 percent of patients), peaked between the ages of 50 and 64, and was more commonly reported by manual workers and persons from rural areas [37].

Etiology

The aetiology of nerve injury is frequently used to classify neuropathic pain. Diabetes (painful diabetic neuropathy (PDN)); shingles (postherpetic neuralgia (PHN)); amputation (stump and phantom limb pain); post-surgery or trauma, stroke, or spinal cord damage; trigeminal neuralgia; and HIV infection are all major causes of neuropathic pain. It's not always clear what's causing the problem. Chronic pain disorders accounted for five of the top 11 diagnoses for years lived with disability in 2010 (Vos 2012), and they cause significant loss of quality of life and employment, as well as increased healthcare expenses. According to a systematic review of papers published since 2000, the total incidence is 7%. Individual countries have recorded incidence rates as high as 8% in the United Kingdom, 6.9% in France, and 3.3 percent in Austria [38].

Management of Neuropathic pain

Rational treatment

Neuropathic pain management focuses on treating symptoms; treating the underlying causes of pain can only be done in certain pathological conditions [39].

- There were 229 studies total in the most current meta-analysis on the effectiveness of the medication.
- Gabapentinoids, tricyclic antidepressants (TCAs), and selective serotonin-norepinephrine reuptake inhibitors (SNRI) were suggested as the first-line treatments for neuropathic pain by the Special Interest Group on Neuropathic Pain (NeuPSIG).
- Strong opioids (Morphine and Oxycodone) and botulinum toxin-A (BTX-A) were included as third-line therapies for peripheral neuropathic pain in addition to lidocaine, capsaicin, and tramadol.

Table 1. Drugs used in the treatment of neuropathic pain

Treatment	Category	Drug	Dose
First-line therapy	Gabapentinoids	Gabapentin	150–600 mg/day
		Pregabalin	300–3600 mg/day
	Tricyclic antidepressants (TCAs)	Amitriptyline	10–150 mg/day
	Serotonin–norepinephrine reuptake inhibitors (SNRI)	Duloxetine	20–120 mg/day
		Venlafaxine	150–225 mg/day
	Opioids	Tramadol	25–400 mg/day

Second-line therapy		Tapentadol	50–600 mg/day
	Topical treatment	Lidocaine	5% patches or gel
		Capsaicin	8% patches
Third-line therapy	Strong opioids	Morphine	10–120 mg/day
		Oxycodone	10–120 mg/day
	Neurotoxin	Botulinum toxin	25–300 U BTX-A 0.9% saline

Emerging treatments under clinical trials

In numerous preclinical and clinical investigations, etamine, memantine, and N-methyl-d-aspartate receptor (NMDAR) antagonists have been used; however, the FDA has not yet approved any of these drugs. Ionotropic glutamate receptors called NMDARs are involved in learning and memory-related activities as well as synaptic transmission and neuroplasticity. NMDARs are under intense investigation as potential therapeutic targets in the treatment of pain because they are altered in several nervous system illnesses, such as neuropathic pain.

- Memantine, a derivative of adamantane, is a non-competitive NMDAR antagonist that has been given the thumbs up for treating Alzheimer's disease by both the FDA and the European Medicines Agency.
- Numerous clinical investigations point to the effectiveness of derivatives of Cannabis sativa in the control of neuropathic pain. A complex plant with about 100 cannabinoids, Cannabis sativa. The delta-9-tetrahydrocannabinol (-9-THC), which has intoxicating characteristics, is the cannabinoid that has been the subject of the most research.
- Recently, an oromucosal spray formulation (Sativex®; GW Pharma Ltd, Salisbury, UK) containing a 1:1 combination of cannabidiol (CBD) and delta-9-THC was created. This formulation is licenced for treating multiple sclerosis spasticity symptoms.
- Neuropathic pain following peripheral injury (NCT00711880; NCT0071054), multiple sclerosis central pain (NCT01604265; NCT00391079), and diabetic neuropathy have all been successfully treated with Sativex in nine clinical trials that were placebo-controlled (NCT00710424).

SCS treatment

Another alternative therapy for those who don't respond to conventional medicine is SCS. Dorsal column stimulation, often known as SCS, is an invasive procedure that includes stimulating the spinal cord's dorsal columns with electrical impulses delivered at rates of about 50 Hz (via an implanted pulse generator) in order to reduce the overexcitability of the brain's neurons. The electrodes can be implanted surgically by a laminotomy or percutaneously using an epidural needle. With a tolerance in the long-term treatment, SCS treatment is effective in about 50% of patients. The stimulation parameters utilised are connected to the induction of paresthesia in the large-diameter fibres in the dorsal column. A number of new electrical factors have been suggested to prevent the paresthesia-related adverse effect [40].

Pregabalin

The pharmacologically active S-enantiomer of a racemic 3-isobutyl gamma amino butyric acid analogue is pregabalin, also known as (S)-3-(aminomethyl)-5-methylhexanoic acid. It is a well-known analgesic and anticonvulsant drug. In fact, pregabalin is the first medication to have its labelling for the treatment of post-herpetic neuralgia and diabetic neuropathy approved by the Food and Drug Administration (FDA) [41]. Pregabalin has been demonstrated to be useful in treating neuropathic pain in preclinical and clinical investigations. Studies on animals have aided in describing the processes underlying the drug's anti-hyperalgesic and anti-allodynic effects. Clinical investigations have also demonstrated pregabalin's effectiveness and dose-dependent effects in treating pain and related symptoms when used alone or in conjunction with analgesics [42][43].

Role of pregabalin in various neuropathic pain

In diabetes linked neuropathic pain

According to three randomised, double-blind, multicenter studies of 5-8 weeks in length involving patients with painful diabetic peripheral neuropathy (pDPN), pregabalin at fixed dosages of 300 and 600 mg/day (three times daily) is reported to be superior to placebo in reducing pain and improving pain-related sleep interference [44]. According to the efficacy findings of a 6-week multicenter study, pregabalin at 600 mg/day considerably lowers the mean pain score and increases the proportion of patients who have a 50% reduction in pain from baseline (39 percent vs. 15 percent for placebo) [45].

Pregabalin monotherapy is preferable in terms of the speed at which pain is reduced, according to a comparison trial of pregabalin (75–300 mg/day), duloxetine (20–120 mg/day), and gabapentin (300–1800 mg/day) in the treatment of diabetic neuropathy for 12 weeks [46]. Pregabalin and gabapentin are both equally effective in reducing pain intensity and improving sleep quality in patients with painful diabetic neuropathy, according to a 6-week research [47].

Pregabalin has been shown to be more cost-effective in the management of refractory diabetic neuropathy than existing treatments (antidepressants, opioids, anticonvulsants other than pregabalin, and/or analgesics), in addition to having better pain-relieving effects [48]. Various other researches have also backed up the usefulness of pregabalin in treating different types of neuropathic pain.

In cancer induced neuropathic pain

Pregabalin may be helpful in treating neuropathic pain brought on by anti-cancer medications (chemotherapy) as well as pain brought on by cancer. Pregabalin (> 300 mg/day) has been shown to be beneficial in reducing neuropathic pain caused by cancer in a retrospective study of Japanese patients [49]. Compared to a combination of the transdermal fentanyl patch, oxycodone, and gabapentin, pregabalin and oxycodone effectively reduced neuropathic pain following chemoradiation therapy in patients with non-small cell lung cancer.

In Post-herpetic Neuralgia (PHN)

Pregabalin (150, 300, and 600 mg/day) was shown to be effective within a week of treatment in two multi-centre, double-blind, placebo-controlled trials with 370 and 238 PHN patients for 13 weeks and 8 weeks, respectively [50]. Mild to moderate side effects included drowsiness, peripheral doema, headache, dry mouth, and ataxia. Pregabalin's effectiveness in lessening pain intensity in individuals with PHN-related neuropathic pain has also been demonstrated by a meta-analysis using the MEDLINE and AMBASE databases.

In Fibromyalgia

An eight-week, multi-centre, double-blind, randomised clinical research showed that pregabalin at varied doses (150, 300, and 450 mg/day) was effective in reducing pain in 529 fibromyalgia patients. Pregabalin was shown to significantly improve the health-related quality of life with tolerable mild to moderate side effects, the most common of which were somnolence and dizziness [51]. It was also shown to significantly reduce the average severity of pain (more patients had >/=50% improvement in pain at the end point, i.e., 29 percent versus 13 percent in the placebo group).

In Trigeminal Neuralgia

Pregabalin (150–600 mg/day) significantly reduces pain intensity and frequency (>50 percent) after 8 weeks in patients with trigeminal neuralgia, whether or not there is concurrent facial pain, according to a one-year follow-up, open label study to assess the efficacy of pregabalin treatment in these patients. Pregabalin may be the medicine of choice for treating trigeminal neuralgia because the pain alleviation lasted for a long time and persisted even after a year [52].

Pre or post operative pain

Pregabalin was shown to be effective and safe in reducing both acute post-operative pain (up to 48 hours after surgery) and chronic pain (measured as hypoesthesia in the anterior chest after 3 months of surgery) in patients after robot-assisted endoscopic thyroidectomy when administered preoperatively (1 hour before surgery) (initial dose 150 mg, followed by Pregabalin was mostly beneficial in lowering early postoperative pain, but not chronic pain, as evidenced by the lack of a significant difference between two groups in regards to chronic pain and chest hypoesthesia after three months following surgery [53].

A number of national and international professional organisations, including the International Association for the Study of Pain [54], the European Federation of Neurological Societies (EFNS), the National Institute for Health and Care Excellence (NICE) of the UK, and the Canadian Pain Society (CPS) [55] have published clinical practise guidelines to help with the assessment and treatment of neuropathic pain.

The recommendations for the pharmaceutical management of neuropathic pain are generally in agreement. Tricyclic antidepressants, especially amitriptyline, SNRIs like duloxetine, and the calcium channel alpha-2-delta ligands gabapentin and pregabalin are three medication families that have earned high recommendations for first-line therapy in all guidelines.

Most guidelines suggest using tramadol, a mild opioid and an SNRI, as a second-line treatment for neuropathic pain. Tramadol is only advised for use in rescue therapy, according to the NICE guidelines, because it is generally linked to higher rates of withdrawal due to adverse events than other treatments and because the clinical studies that looked into its efficacy involved few patients and had observation periods of up to four weeks [56].

Strong opioids, non-gabapentinoid antiepileptic medications, and cannabinoids are frequently prescribed as third- and fourth-line medications. Trigeminal neuralgia can be effectively treated with carbamazepine, according to general consensus. For localised neuropathic pain, topical formulations of capsaicin and lidocaine are advised.

Mode of action

Pregabalin is a calcium channel antagonist that has a particular affinity for the auxiliary subunits (2- and 2-2) of voltage-dependent calcium channels, especially P/Q, N, and L-type [57][58]. Studies using transgenic mice bearing a mutant CaV 2-gene provide the strongest evidence for 2- being the main target of pregabalin (R217A mutant mice). Pregabalin's binding affinity was dramatically reduced in the cortex (by 84 percent), hippocampus (by 80 percent), caudate putamen (by 66 percent), lumbar dorsal horn (by 70 percent), and cerebellum (by 37 percent) of R217A animals, according to the autoradiographic investigation. Pregabalin's analgesic effect was also discovered to be eliminated in these mutant mice (in both the CCI and formalin test), with no effect on the analgesic activity of morphine or amitriptyline, demonstrating the significance of pregabalin's binding to the 2--1 subunit of VDCC for its analgesic activity [59].

It has been demonstrated that pregabalin may affect a variety of potassium channels, including KATP channels, which suggests yet another mechanism for how it works as an analgesic. By lowering neuronal excitability and preventing the release of many neurotransmitters, including substance P in the spinal cord, KATP channel opening is said to have anti-nociceptive effects [60].

Despite having a structural similarity to GABA, pregabalin has not been discovered to be converted into GABA and does not have a direct affinity for GABA receptors. Pregabalin does not seem to pharmacologically augment or imitate GABA, indicating that its pharmacological effects are not greatly influenced by direct or indirect effects on GABA receptors. Pregabalin has no interaction for GABA-A or GABA-B receptors, according to radioligand binding experiments [61]. Pregabalin's antiallodynic efficacy was unaffected by pretreatment with bicuculline, a GABA-A antagonist, indicating that its therapeutic action is not conducted through GABA-A receptors [62].

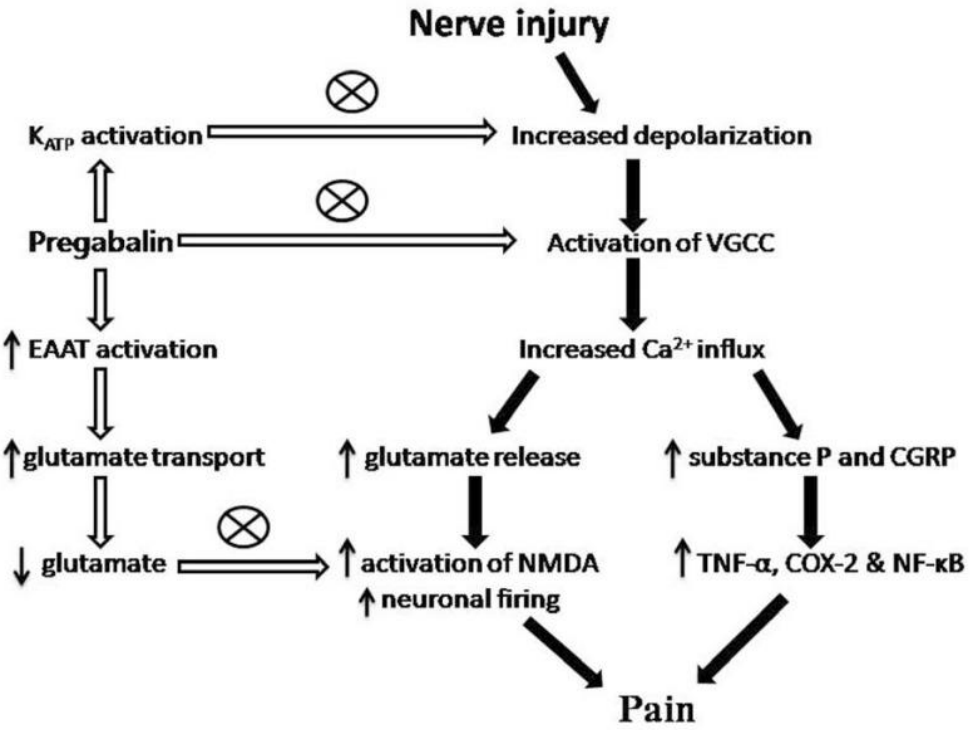

Fig 2. Depiction of mode of action of pregabalin in neuropathic pain

In inflammation-induced spinal cord sensitization, pregabalin affects the release of sensory neuropeptides such substance P and CGRP [63]. Pregabalin's neuroprotective impact is likely mediated by an anti-inflammatory effect, as evidenced by the fact that it suppresses lipid peroxidation, microglial cells, and attenuates cellular death, particularly in oligodendrocytes [64]. Pregabalin inhibits p65 nuclear localization, which prevents substance P and other inflammatory neuropeptides from inducing NF-kB activation in both neuronal and glial cell lines. Pregabalin also reduces the expression of COX-2 and NF-kB-regulated gene products, which prevents substance P from causing the manufacture of cytokines in a variety of neurological illnesses [65].

Conclusion

Mucoadhesive patches were developed in novel drug delivery system to increase the bioavailability and reduce the systemic toxicity. This review emphasizes on the critically acknowledge the polymers used in mucoadhesive formulation, mechanism of cohesion, main method of preparations (solvent casting & milling), advantages & disadvantages of mucoadhesive patches.

Longer adhesion at target site, minimized metabolic activity and patient acceptance are all advantages of mucoadhesive dosage forms. The choosing of a convenient polymer with better mucosal-adhesive feature and biocompatibility is essential in development of mucoadhesive patch [35].

However, delivering therapeutically for the therapy of both systemic and topical disorders would take a lot more work with these innovative mucoadhesive formulations. In conclusion,

it facilitates the target therapy by enriching efficacy or intrinsic activity. It has proved a pathway for rapid and systemic potential of mucoadhesive substances. So, this route has become essential in the case of emergency treatment.

Pregabalin is expected to have a very favourable safety profile and be a very effective treatment for neuropathic pain, according to preclinical and clinical studies. Pregabalin's action is most likely to inhibit voltage-gated Ca2+ channels, which helps to decrease the production of excitatory neurotransmitters and impede synaptic transmission. Other potential pathways for its analgesic effects include inflammation, excitatory amino acid transporter regulation, and K+ channel conductance modulation. Studies are still required to clarify its process in more depth, though.

Neuropathic pain is a common condition that has an adverse effect on individuals who experience it. Although a number of professional organisations have developed clinical practise guidelines for the diagnosis and management of neuropathic pain, their applicability in everyday clinical practise is constrained by a number of methodological and conceptual issues. These limitations also affect the validity of the evidence on which these guidelines are based. To address the present challenges surrounding the treatment of neuropathic pain, including the low efficacy of pain management and the poor QoL in people affected, innovative pharmacological therapies must be developed.

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Conflict of Interest

Authors have declared for none conflict of interest.

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