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Research Article

Preparation And Evaluation Of Transdermal Patch Of Lacosamide For Epilepsy

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ABSTRACT

The primary aim of the work is preparation, characterization, and evaluation of lacosamide used for formulation of transdermal patch for antiepileptic activity. Then optimization of lacosamide for comtrol relese action using central composite design[CCD] In this study, we present a state-of-the-art review of the neuro physiological view of epilepsy as a disease affecting neural networks.We describe the basic and advanced principles of epilepsy as a disease affecting neural networks, based on the use of different clinical and mathematical techniques from a neurophysiological perspective, and signal the limitations of these findings in the clinical context. The patient of Epilepsy disease, they does not able to take medicine on time because of seizures may occurs in clusters ,loss of consciousness repeatedly for this purpose long acting transdermal patches are prepared.

Objectives:

1. In this study, we present a state-of-the-art review of the neuro physiological view of epilepsy as a disease affecting neural networks.
2. We describe the basic and advanced principles of epilepsy as a disease affecting neural networks, based on the use of different clinical and mathematical techniques from a neurophysiological perspective, and signal the limitations of these findings in the clinical context.

INTRODUCTION

Transdermal patch generally refers to topical application delivers agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. World Journal of Pharmaceutical Research SJIF Impact Factor 8.074 Volume 7, Issue 16, 1101-1115. Research Article ISSN 2277– 7105 *Corresponding Author D. Maheswara Reddy Santhiram College of Pharmacy, Nandyal. Article Received on 01 July 2018, Revised on 21 July 2018, Accepted on 11 August 2018, DOI: 10.20959/wjpr201816-13183 www.wjpr.net Vol 7, Issue 16, 2018. 1102 Reddy

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et al. World Journal of Pharmaceutical Research Transdermal Patch offers many advantages over the conventional dosage forms or controlled release oral systems. Transdermal patch provides constant blood levels, avoids first pass metabolism, increased patient compliance, and avoids dose dumping.[1,2] Transdermal drug delivery systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin, at a controlled rate to the systemic circulation.[3] Lacosamide (LC) is a novel antiepileptic drug (AED) and its mechanism of action distinguishes it from other AEDs. Unlike classical AEDs like phenytoin or carbamazepine which affect fast inactivation, LC enhances sodium channel slow inactivation. This results in stabilization of neuronal membranes and decrease in neuronal firing [1]. It has been suggested that the drug also binds to collapsin response mediator protein 2 (CRMP-2) which plays a role in neuronal differentiation. Collapsin response mediator protein 2 is associated with the development of epilepsy, but its role is not fully clear . Latest study indicates that CRMP-2 is also linked to the addiction-like behavior and LC can reduce the hippocampal CRMP-2 level in ethanol-addicted mice . However, another study indicated that the drug does not specifically bind to human CRMP-2 [4]. An important part of the mechanism of action of LC is its neuroprotective activity. The drug reduced the production of reactive oxygen species by increasing the expression of antioxidant enzymes and inhibiting lipid peroxidation [5]. It has been also shown that LC has a neuroprotective effect on the hippocampus which is a brain structure associated with memory processes [6]. Other studies also indicated the neuroprotective effect of LC on the hippocampus [7,8]. It is an important observation because memory disturbances can be not only a secondary effect of epilepsy or other central disorders but also a side effect of AEDs

Topical Drug Delivery System

Topical formulations contain an active ingredient, often a medication or drug or botanical, and a vehicle. The vehicle usually contains water, oil, alcohol or propylene glycol mixed with preservatives, emulsifiers, absorption promoters and fragrances. The table below describes different formulations.

Controlled Drug Delivery Systems: Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue.4 Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.

1. Delayed release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting

More precisely, controlled delivery can be defined as:-

1. Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
2. Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.
3. Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.
4. Provide physiologically/therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.

Epilepsy

Epilepsy is a chronic central nervous system disorder that occurs not only with the imbalance of

glutamatergic neurons and inhibitory gamma-aminobutyric acid (g-GABA) neurons, but also with abnormal Central cholinergic neuronal regulation. Since long term usage of antiepileptic drugs cause high incidence of pharmacoresistance and untoward side effects, attention has been paid in recent years to screen bioactive compounds from natural medicinal plants for the treatment of several neurological disorders including Epilepsy. Keeping in view of relative importance of natural medicinal plants, the present study is mainly focused to characterize the anti-convulsant effect of Bacopa monnieri (BM), an Indian herb which is being extensively used in Ayurvedic treatments related to neurological complications. The present study is designed to assess the neurotoxicity of Pentylene tetrazole (PTZ), an epileptic compound with particular reference to Cholinergic system and ATPases in different brain regions of rat to explore the possible antiepileptic effect of different extracts of BM in comparison with Diazepam (DZ) (Reference control). The activity levels of Acetyl cholinesterase (AChE) and ATPases were decreased in different regions of brain during PTZ induced epilepsy which were increased in epileptic rats pretreated with different extracts of Bacopa monnieri except EAE and AE. In addition Acetylcholine (ACh), levels were increased during PTZ induced epilepsy when compared with normal control and levels were reversed on pretreatment with different extracts of BM. Recoveries of these parameters suggest that the bioactive factors present in the extracts offer neuroprotection by interrupting the pathological cascade that occurs during epileptogenesis.[10]

Lacosamide

The complicated dosing regimens required by many immediate release (IR) ASMs (such as twice- or three-times-daily dosing) commonly cause partial adherence to dosing routines, which can negatively affect seizure control (Getnet et al., 2016). Extended-release (XR) ASM formulations may offer clinical advantages over IR formulations by simplifying dosing routines to once per day, thereby increasing patient adherence and improving clinical outcomes (Hovinga et al., 2008; Wheless and Phelps, 2018). XR formulations are often better tolerated than IR formulations, as they can result in more gradual increases in drug plasma concentrations and potentially lower maximum concentrations (Cmax) (Wheless and Phelps, 2018). Lacosamide (LC) is a novel antiepileptic drug (AED) and its mechanism of action distinguishes it from other AEDs. Unlike classical AEDs like phenytoin or carbamazepine which affect fast inactivation, LC enhances sodium channel slow inactivation. This results in stabilization of neuronal membranes and decrease in neuronal firing . It has been suggested that the drug also binds to collapsin response mediator protein 2 (CRMP-2) which plays arole in neuronal differentiation. Collapsin response mediator protein 2 is associated with the development of epilepsy, but its role is not fully clear . Latest study indicates that CRMP-2 is also linked to the addiction-like behavior and LC can reduce the hippocampal CRMP-2 level in ethanol-addicted mice . However, another study indicated that the drug does not specifically bind to human CRMP-2 . An important part of the mechanism of action of LC is its neuroprotective activity. The drug reduced the production of reactive oxygen species by increasing the expression of antioxidant enzymes and inhibiting lipid peroxidation .

Advantages

1. Make it more bioavailable.
2. Cut down on how often you dose.
3. The drug delivery method is painless and doesn't hurt.
4. Stay away from liver first pass metabolism.
5. Get patients to follow through more often, especially kids and older people.
6. They offer long-lasting treatment with just one dose.

7. Medication that can be taken by itself[11][12]
8. Transdermal Nitroglycerin is one way to avoid the first pass impact. When taken by mouth, it is quickly broken down by the liner.
9. The drugs that have a half-life at the start of the therapy can work for longer because they are stored and released slowly over time.
10. The treatment with drugs can be stopped quickly by taking off the skin product.[13][14]

Disadvantages

1. Small amount of the drug is put on the skin.
2. Itching of the skin may happen.
3. The amount of drug in the blood cannot get very high.
4. Costs more.
5. You should not take an electric drug.[15][16]
6. We can only use strong drugs in transdermal patches because the skin naturally limits how much of the drug can get through.
7. Some drugs, like scopolamine, have a skin patch that is put behind the ear, which is painful.
8. Adhering for a long time is hard.[17][18]

Applications

1. A nicotine patch that you put on your skin. This patch releases nicotine in controlled amounts to help you stop smoking.
2. Sometimes, nitroglycerine patches are also given to people with Angina to help them feel better.
3. Transdermal patches are another way to get clonidine, a drug used to treat high blood pressure, and ketoprofen, a non-steroidal anti-inflammatory drug.
4. An antidepressant called selegiline, an MAOI, was the first drug to be delivered through the skin.
5. Transdermal release agent for ADHD.
6. Instead of pills that are put under the tongue, nitroglycerin patches are sometimes given to treat angina.
7. Transdermal scopolamine is often used to help people who are sick from motion.
8. A topical patch form of the blood pressure medicine clonidine is available.
9. 9)In 2007, the drug Rivastigmine, which is used to treat Alzheimer's, came out as a patch under the brand name Exelon.
10. 10) Caffeine patches, which are made to get caffeine into the body through the skin.[19]

Limitations of TDDS

1. Skin that isn't very permeable.
2. Only allowed for powerful drugs.
3. Not good for molecules that are bigger than 500 Daltons
4. 4)This method can't be used for drugs that melt easily because they don't mix well with water or fat.
5. They're not good at all if they make your skin itch.
6. Ionic drugs can't be sent through this method.[20]

Central composite Design

Central composite design (CCD) is one of the tools used to study the effect of different variables on the dependent variables of any formulation. Based on the principle of design of experiments, CCD was employed to investigate the effect of two independent factors. Design of experiments encompasses the use of various types of experimental designs, generation of polynomial equations, and responses over the experimental domain to determine the optimum formulation. Multiple linear regression analysis of results leads to equations that adequately described the influence of the independent variables on the selected responses .

Literature Review

1.Keurentjes et al.,

2019,worked on the risk evaluation of dermal experience, extrapolative numerical models are used. In this exertion the accurateness to predict flux of the model is judged against experimental

human in vivo data of drugs practical in US-FDA approved TDS. A record of pharmacokinetic statistics of drugs practical in TDS was used and updated. Three mathematical models (QSAR) were used to analyze envisage fluxes, and compared to the human in vivo data. For more than half of the drugs applied in TDS, the forecast flux by the numerical models was at par comparable to the flux designed with the experimental in vivo data. The flux was more than- or underestimate factor 10–100. All numerical models were appreciably correlated with the in vestigational in vivo data. The development of percutaneous penetration has numerous influencing factors, TDS minimize some of these reasons.

2.Ameen and Michniak-Kohn., 2019, offers an optional course of drug

administration mainly for Alzheimer's disease patients from beginning to end which abolish gastrointestinal side effects and eventually improving compliance. They organized optimized matrix type patches of galantamine for the transdermal delivery and performed ex vivo and in vitro estimation. Four pressure sensitive adhesive with dissimilar functional groups, ten diffusion enhancers and four drug loadings were experimented to devise the optimized patch. The ex vivo penetration of the dissimilar formulated patches from end to end human cadaver skin by means of Franz diffusion examined

3.Ifeoma and Kevin., 2019,worked on hypokalemia which is one of the

majority and frequent type of electrolyte difference. Its defined as a serum potassium level of ≤3.5 mEq/L. Potassium is important for proper nerve and muscle excitation. Presently, there are a number of potassium supplements, but they are affected by several shortcomings e.g. oral potassium tablets require a longer time to attain peak plasma concentration and parenteral administration can cause pain, swelling, trypanophobia with risk of hyperkalemia. Knowing these harms, it is decisive to extend a fitting substitute for potassium supplementation. Transdermal drug delivery is a hopeful alternative. route has bulky plane vicinity which can be used for drug supervision and has the facility to impart sustained-release goods that can help sustain potassium levels. The intention of this assignment was to explore the effect of pressure of micro needle rollers on the infiltration of potassium chloride transversely through porcine skin. Permeation studies were accepted away in vitro using the Franz diffusion apparatus. The trans dermal change of potassium chloride was investigated using inductively attached plasma visual emission spectrometry. Micro channel categorization was accepted away by means of digital microscopy, bright field stereomicroscopy and confocal laser scanning microscopy. This indicates trans dermal change of potassium chloride achieved via passive diffusion whereas this suggest trans dermal change of potassium chloride achieved via micro needle-enhanced permeation.

4.Ameen and Michniak-Kohn., 2019, offers an optional course of drug

administration mainly for Alzheimer's disease patients from beginning to end which abolish gastrointestinal side effects and eventually improving compliance. They organized optimized matrix type patches of galantamine for the transdermal delivery and performed ex vivo and in vitro estimation. Four pressure sensitive adhesive with dissimilar functional groups, ten diffusion enhancers and four drug loadings were experimented to devise the optimized patch. The ex vivo penetration of the dissimilar formulated patches from end to end human cadaver skin by means of Franz diffusion cells examined.

5.Geile et al., 2019,

worked on fentanyl is an effective copied opioid with amultiplicity of promising application. Transdermal fentanyl patches are repeatedly

prearranged for patients with rigorous chronic or cancerrelated pain. The possiblity for mistreatment is well-known and dangers linked with illicit fentanyl ingestion are serious. Fentanyl toxicity due to accidental mistreatment is comparatively uncommon. This study listedcarefully all such examples and their importance in forensic assessmentand put in new parameters and study the obtainable femoral blood in the occasion of critical fentanyl patch misapplications. the molecules and therefore merely a small fraction of little molecules are allowed to assess the site of action. A original form of modification called the microneedles help to augment the penetration of the preparation throughout skin course and prevent a variety of harms connected with the conservative formulations. The main formulation occupy folds of the skin and get deposited, therefore generate micron size conduit that directthe drug straight to the epidermis or superior dermis section from wherethe drug can go into the circulation by passing the obstacle. There are avariety microneedles which can be fictitious like solid, dissolving,hydrogel, coated and hollow micro needles. Production technique chosen depends on the kind and fabric of the micro needle. Ramadan et al., 2018, invented a elastic matrix type transdermal patch of lamivudine having monolithic polymeric film as an endeavor tosolve the problems like biological small half-life and fluctuations in plasma concentration with oral dose. They examined the film organoleptically, physicochemical properties, their ex vivo permeation, in vivo pharmacokinetic parameters.

6.Zhou et al., 2018,distribute drugs all the way through the exterior of the skin for local or general administration. The drug absorption after inclusion all the way through the skin into the systemic circulation via vessel achieved at a definite rate by use of time-honored substantial and element enhancers to increase the transdermal permeation rate by increasing drug solubility, diffusion coefficient. Adverse consequence is not practicable control and increase in level of drug to toxic levels. Due to excess of penetration enhancers. Nano-formulations normally diverge insize and range from 10 nm to 100 nm. The smaller particle size result in improved permeability, stability, retention, and targeting, making nanoformulations appropriate for transdermal drug delivery. The different applications of nano-formulations (vesicles or nanoparticles and nanoemulsions) have been widely studied.

7.Kriplani et al., 2018,prepared and evaluated transdermal films of non steroidal anti-inflammatory drug. They prepared three transdermal patches using various concentrations of ethyl cellulose. They concluded that as the concentration of polymer enhance the thickness of patch, weight uniformity and folding endurance also enhance.

8.Emma et al., 2018, formulated patches of Ibuprofen drug using a poly ether- urethane-silicone crosslinked as the drug reservoir using solvent less process. They prepared patch also prepared hot-melt crosslinking technique at 75°c in 90% relative humidity lacking the accumulation of solvents. The formulations characterized such as dissolution and permeation studies with utilizing diffusion cells. The method for estimation was validated by HPLC methods to determine the drug content. The formulations also estimated by accelerated stability studies at 35°c with 60% relative humidity.

9.Szunerits and Boukherroub et al., 2018, reviewed the development in this field of transdermal drug delivey system. They also summarized examples of thermal technologies for local and systemic transdermal drug delivery. They reviewed execution of the novel approaches and its methods to conquer limitation for passive diffusion without altering skin integrity.

10.Verma et al., 2017, reviewed various evaluation methods for transdermal dosage for. They also discussed recent advancement in development of Transdemal drug delivery system. They discussed that TDDS is expensive substitute of conventional formulation.

11.Kattiet al., 2017 formulated and developed transdermal patch of Tizanidine Hydrochloride to overcome the limitation of bioavailability. They found that, Moringa oleifera gum has potential to modify drug release rate and having good film former and adhesive property. The transdermal patch revealed promising drug release within 12 hr (84.36%), good stability and no irritancy.

12.Siji et al., 2016, investigated the result of backing films on transdermal delivery of cyclobenzaprine patch. Diverse backing films were selected to arrange the cyclobenzaprine transdermal patch. The cumulative amount of cyclobenzaprine at large from diverse patches was appraise in vitro. To examine the communication flanked by cyclobenzaprine and backing films, the separation trial and attenuated total reflectance Fouriertransform infrared (ATR-FTIR) spectroscopy were execute. The cumulative quantity of cyclobenzaprine released beginning the patch with Cotran™ 9700 as backing film. The quantity of cyclobenzaprine out beginning the patch with Cotran™ 9700 as backing film diminish radically after 7 d storage at room circumstance. The division experiments specify a strapping adsorption of cyclobenzaprine onto the Cotran™ 9700, which could explicate the dwindle of cumulative quantity of cyclobenzaprine free beginning the patch with Cotran™ 9700 as backing film.

13.Indulekha et al., 2016, planned a temperature generate transdermal drug deliverance system (TDDS) with a thermo responsive polymer, poly(N-vinyl caprolactam) [PNVCL] support gel, someplace in patients canthemselves govern a pulsate of treatment on simple purpose of heat padlarger than the TDDS. The phase alteration heat of PNVCL was adjust to35 °C by embed it onto a pH sensitive biopolymer, Chitosan, to produce

14.Chitosan-g-PNVCL (CP) co-polymer which render the gel mutually thermo- and pH-responsive belongings. The submission of triggered delivery was explored by consignment acetamidophenol (a model hydrophilic drug) and etoricoxib (a model hydrophobic drug). In vitro drug discharge experiments were achieved at three unusual temperature (25, 32 and 39 °C) at two different pH (5.5 and 7) to study its drug release with answer to heat and pH. In vitro skin permeation of both the drugs demonstrate enhanced drug liberate at what time the covering was subjected to superior temperature (39 °C). Furthermore, it was also institute that coat infiltration for hydrophobic drug was superior than that of hydrophilic drug. The in vivo biocompatibility learning of the CP gel in rat coat proves that the gel is biocompatible. The results attain confirmed the potential employ of the thermo responsive CP gel as an ondemand restricted drug delivery arrangement. Narasimhulu et al., 2015, include various mechanisms, working process of transdermal film, application of penetration enhancers, different evaluations parameters etc.

15.Thejeswi et al., 2015, developed the transdermal patch using hydrophilic polymer of drug containing amphotericin B. Hydrophilic polymer applied to increase the bioavailability as approaches developed as penetrating poorly water soluble compounds.

16.Zhang et al., 2014,evaluated transdermal patch for identified organic matrices of drug excipient interaction process. Organic amines salt use for permeation enhancing for Diclofenac and was tested in vitro usingexcised rabbit skin as transdermal barrier in two-chamber diffusion cell.They optimized concentration of percutaneous

permeation enhancer and the loading dose of drugs. The result indicated that skin penetration of Diclofenac triethylamine salt was better than other organic amine salts. Singh et al., 2014, formulated placebo transdermal patches by using different polymers like ethyl cellulose, poly vinyl pyrrolidone and eudragit by solvent evaporation techniques. The formulations were characterized with a different number of parameters. The tensile strength, foldingendurance of prepared films was shown high plasticity in variouscombinations of polymers. The result easily concluded that the Di-nbutylphthalateat concentration 20% of polymers used as plasticizer for further developmental studies.

17.Banerjee et al., 2014,prepared "patches," intended to transport a therapeutically efficient quantity of drug crosswise the skin. The superiority characteristic of the adhesive in TDDS is indispensible for manufacture intend and imperative to the protection, usefulness and superiority estimate of the concluding creation. Progress in the pasture of bonding agent knowledge has smoothed the technique for scheming TDDS that have extensive elasticity.

18.Agrawal et al., 2010, reviewed various transdermal formulations of psychotropic substance with methods and advantages. They state that effective therapeutic effect of drug need proper drug selection. New drug administration methods are investigated for better patient compliance and to increase drug effect in low dose. oral administration of psychotropic drugs is not suitable for psychiatric patients due to noncompliance.Preparation of transdermal patch of psychotropic drug is better option to improve patient compliance. Transdermal patches are better option for management of pain, pregnancy prevention and hormone replacement therapy. They have many advantages over conventional oral therapies. Transdermal patches provide continuous drug delivery resulting improve tolerability. Psychotropic drugs like Selegiline, fluoxetine, haloperidol, imipramine, methylphenidate and rivastigmine have been formulated as transdermal systems. New improvements with the use of permeation enhancers, transdermal gels, iontophoresis, electroporation and sonophoresis are better technologies for formulation of transdermal drug delivery of psychotropics substance.

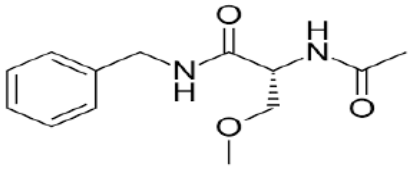
19.Bhaskar et al., 2010,compared the oral Diclofenac tablets and transdermal Diclofenac patch for multiple premolar extractions inorthodontic treatment. They concluded that the transdermal Diclofenacpatch offer potent analgesia compared to conventional therapy for betterpatient compliance. This may be used as analgesia for schedule post extraction

20.Kumar et al., 2006,characterized UV spectroscopic method for quantification of Diclofenac Potassium and Tizanidine in tablet. They validated new analytical methods based on the simultaneous estimation of drugs in a binary mixture without previous separation. The binary mixture was determined by mixed standards and three sampling wavelengths of 277 nm, 295 nm (isobestic point), and 320 nm in multiwavelength technique. The drugs were calculate approximately by using the absorptivity values of Diclofenac Potassium and Tizanidine at elected wavelengths of multiwavelength technique and simultaneous equation method separately. These three developed methods were required no separation, simple, accurate, rapid method used for quality control analysis of both drug.

DRUG PROFILE

Lacosamide

1. Name oF Drug: Lacosamide
2. Chemical Formula: C13H18N2O3
3. IUPAC Name: N2-acetyl-N-benzyl-D-homoserinamide
4. Molecular Weight: 250.294 g/mol
5. Chemical Structure:



Melting Point:143-144°C

CLINICAL PHARMACOLOGY

Mechanism of Action

The precise mechanism by which lacosamide exerts its antiepileptic effects in humans remains to be fully elucidated. In vitro electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing.

1. Generic Name: Vimpat (Vim-pat)
2. Drug Class: Anticovulsants
3. Therapeutic Class: CYP3A4 inhibitors
4. Similar Drugs: levetiracetam

Pharmacokinetics

The pharmacokinetics of lacosamide have been studied in healthy adult subjects (age range 18 to 87), adults with partial-onset seizures, adults with diabetic neuropathy, and subjects with renal and hepatic impairment. The pharmacokinetics of lacosamide are similar in healthy subjects, patients with partial-onset seizures, and patients with primary generalized tonic-clonic seizures. Lacosamide is completely absorbed after oral administration with negligible first-pass effect with a high absolute bioavailability of approximately 100%.

Pharmacodynamics

A pharmacokinetic-pharmacodynamic (efficacy) analysis was performed based on the pooled data from the 3 efficacy trials for partial-onset seizures. Lacosamide exposure is correlated with the reduction in seizure frequency. However, doses above 400 mg/day do not appear to confer additional benefit in group analyses. Cardiac Electrophysiology Electrocardiographic effects of lacosamide were determined in a double-blind, randomized clinical pharmacology trial of 247 healthy subjects. Chronic oral doses of 400 and 800 mg/day (equal to and two times the maximum daily recommended dose, respectively) were compared with placebo and a positive control (400 mg moxifloxacin). Lacosamide did not prolong QTc interval and did not have a dose-related or clinically important effect on QRS duration

Absorption and Bioavailability

Lacosamide is completely absorbed after oral administration. The oral bioavailability oflacosamide tablets is approximately 100%. Food does not affect the rate and extent of absorption. After intravenous administration, Cmax is reached at the end of infusion. The 30- and 60- minute intravenous infusions are bioequivalent to the oral tablet. For the 15-minute intravenous infusion, bioequivalence was met for AUC.

EXCIPIENT PROFILE

PHARMACEUTICAL EXCIPIENTS

1. HPMC
2. PEG
3. PROPYLENE GLYCOL
4. METHANOL
5. CHLOROFORM

1. HPMC

Hydroxy Propyl Methyl Cellulose [HPMC] [Hypromellose Phthalate]

Fig.No.1

2. Synonyms:

Cellulose phthalate hydroxypropyl methyl ether; HPMCP; hydroxypropyl methylcellulose benzene-1,2-dicarboxylate; 2-hydroxypropyl methylcellulose phthalate; hypromellosi phthalas;

Mantrocel HP-55; methylhydroxypropylcellulose phthalate..

3. Chemical Name and CAS Registry Number:-

Cellulose, hydrogen 1,2-benzenedicarboxylate, 2-hydroxypropyl methyl ether [9050-31-1]

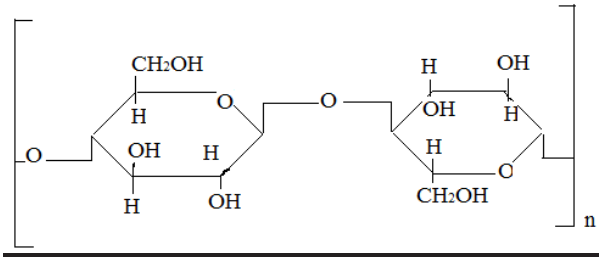
4. Empirical Formula and Molecular Weight

Hypromellose phthalate is a cellulose in which some of the hydroxyl groups are replaced with methyl ethers, 2-hydroxypropyl ethers, or phthalyl esters. Several different types of hypromellose phthalate are commercially available with molecular weights in the range

20 000–200 000. Typical average values are 80 000–130 000.(1).

1. **Empirical formula And Structural Formula:-**

C56H108030



6. Functional Category:-

Coating agent.

Hypromellose phthalate occurs as white to slightly off-white, freeflowing flakes or as a granular powder. It is odorless or with a slightly acidic odor and has a barely detectable taste.

15. Regulatory Status:-

Included in the FDA Inactive Ingredients Database (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

16. Related Substances:-

Cellulose acetate phthalate; hypromellose.

2.PEG

Polyethylene Glycol

1 Nonproprietary Names

BP: Macrogols

JP: Macrogol 400

Macrogol 1500

Macrogol 4000

PhEur: Macrogols

USP-NF: Polyethylene Glycol

2 Synonyms

Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; macrogola; PEG; Pluriol E; polyoxyethylene glycol.

Fig.No.2

3 Chemical Name and CAS Registry Number

a-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl) [25322-68-3]

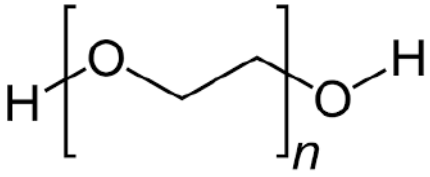
4 Empirical Formula and Molecular Weight

HOCH2(CH2OCH2)mCH2OH where m represents the average number of oxyethylene groups. Alternatively, the general formula H(OCH2CH2)nOH may be used to represent polyethylene glycol, where n is a number m in the previous formula

þ 1. See Table I for the average molecular weights of typical polyethylene glycols.

Note that the number that follows PEG indicates the average molecular weight of the polymer.

5 Structural Formula



6 Functional Category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations, including parenteral, topical, ophthalmic, oral, and rectal preparations. Polyethylene glycol has been used experimentally in biodegradable polymeric matrices used in controlled-release systems. Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin; see Section 14. They do not readily penetrate the skin, although the polyethylene glycols are watersolubleand are easily removed from the skin by washing, making them useful as ointment bases. Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol. Mixtures of polyethylene glycols can be used as suppository bases, for which they have many advantages over fats.

8 Description

The USP32–NF27 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures. Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free flowing milled powders.

3.Propylene Glycol

1 Nonproprietary Names

BP: Propylene Glycol

JP: Propylene Glycol

PhEur: Propylene Glycol

USP: Propylene Glycol

2 Synonyms

1,2-Dihydroxypropane; E1520; 2-hydroxypropanol; methyl ethyl

Fig.No.3

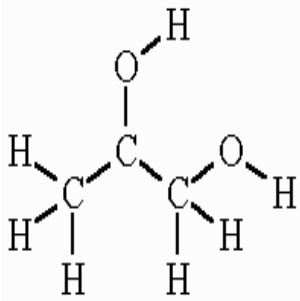
5 Structural Formula

Functional Category

Antimicrobial preservative; disinfectant; humectant; plasticizer; solvent; stabilizing agent; water-miscible cosolvent.

Applications in Pharmaceutical Formulation or **Technology**

Propylene glycol has become widely used as a solvent, extractant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations. It is a better. general solvent than



Description

Propylene glycol is a clear, colorless, viscous, practically odorless liquid, with a sweet, slightly acrid taste resembling that of glycerin.

10 Typical Properties

Autoignition temperatu-3718C

Density -1.038 g/cm3 at 208C

Flammability -Upper limit, 12.6% v/v in air; lower limit, 2.6% v/v in air.

Flash point -998C (open cup)

Heat of combustion -1803.3 kJ/mol (431.0 kcal/mol)

Heat of vaporization -705.4 J/g (168.6 cal/g) at b.p.

Melting point -598C

4.METHANOL

Nonproprietary Names

BP: Racementhol

JP: dl-Menthol

PhEur: Menthol, Racemic

USP: Menthol

Synonyms

Hexahydrothymol;2-isopropyl-5-methylcyclohexanol;4-isopropyl1methylcyclohexan-3-ol; 3-p-menthanol; p-menthan-3-ol; dl menthol; mentholum

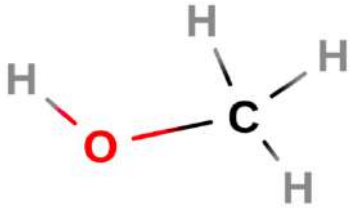
Fig.No.4

5 Structural Formula

Functional Category

Flavoring agent; therapeutic agent.

Applications in Pharmaceutical Formulation or Technology Menthol is widely used in pharmaceuticals, confectionery, and toiletry products as a flavoring agent or odor enhancer. In addition to its characteristic peppermint flavor, lmenthol, which occurs naturally, also exerts a cooling or refreshing sensation that is exploited in many topical preparations. Unlike mannitol, which exerts a similar effect due to a negative heat of solution,



Methanol

When administered orally in small doses menthol has a carminative action.8 Description Racemic menthol is a mixture of equal parts of the (1R,2S,5R)- and (1S,2R,5S)-isomers of menthol. It is a free-flowing or agglomerated crystalline powder, or colorless, prismatic, or acicular shiny crystals, or hexagonal or fused masses with a strong characteristic odor and taste. The crystalline form may change with time owing to sublimation within a closed vessel. The USP 32 specifies that menthol may be either naturally occurring l-menthol or synthetically prepared racemic or dl-menthol. However, the JP XV and PhEur 6.0, along with other pharmacopeias, include two separate monographs for racemic and l-menthol.

LD50 (rat, IM): 10.0 g/kg(9)

LD50 (rat, oral): 3.18 g/kg

Handling Precautions

May be harmful by inhalation or ingestion in large quantities; may be irritant to the skin, eyes, and mucous membranes. Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, chemical resistant gloves, and respirators are recommended. Avoid prolonged or repeated exposure.

Regulatory Status

Included in the FDA Inactive Ingredients Database (dental preparations, inhalations, oral aerosols, capsules, solutions, suspensions, syrups, and tablets; also topical preparations). Included in nonparenteral medicines licensed in the UK. Accepted for use in foods and confectionery as a flavoring agent of natural origin. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

5.CHLOROFORM

Chloroform, or trichloromethane (often abbreviated as TCM), is an organic compound with the formula $CHCl_3$ and a common solvent. It is a very volatile, colorless, strong-smelling, dense liquid produced on a large scale as a precursor to refrigerants and PTFE. Chloroform is a

trihalomethane that serves as a powerful anesthetic, euphoriant, anxiolytic, and sedative when inhaled or ingested. Chloroform was used as an anesthetic between the 19th century and the first half of the 20th century. It is miscible with many solvents but it is only very slightly soluble in water (only 8 g/L at 20°C).

Fig.No.5

In chemical nomenclature, a preferred IUPAC name (PIN) is a unique name, assigned to a chemical substance and preferred among all possible names generated by IUPAC nomenclature. The "preferred IUPAC nomenclature" provides a set of rules for choosing between multiple possibilities in situations where it is important to decide on a unique name. It is intended for use in legal and regulatory situations.Preferred IUPAC names are applicable only for organic compounds, to which the IUPAC has the definition as compounds which contain at least a single carbon atom but no alkali, alkaline earth or transition metals and can be named by the nomenclature of organic compounds (see below). Rules for the remaining organic and inorganic compounds are still under development. The concept of PINs is defined in the introductory chapter and chapter 5 of the "Nomenclature of Organic Chemistry: IUPAC Recommendations and Preferred Names 2013" (freely accessible), which replace two former publications: the "Nomenclature of Organic Chemistry", 1979 (the Blue Book) and "A Guide to IUPAC Nomenclature of Organic Compounds, Recommendations 1993". The full draft version of the PIN recommendations ("Preferred names in the nomenclature of organic compounds", Draft of 7 October 2004) is also available.]

MATERIALS AND EQUIPMENTS

Material:-

Lacosamide was received as a gift sample from MEDLEY PHARMACEUTICALS LTD.MUMBAI. And HPMC ,PEG,Propylene Glycol ,Methanol and Chloroform all other chemicals were of analytical grade.

EQUIPMENTS

Sr. No.	Instruments
1	UV Spectrophotometer
2	FTIR Spectrophotmeter
3	Sonicator
4	Electronic Weighing Balance
5	Magnetic Stirrer

Experimental Work

Preformulation study:

1. **Melting point**

The melting point is determine by using manual physical methods using Thieles tube and liquid paraffin.

The melting point is typically around143-144°C.

Sr.no	Drug samples	Temperature(oC)
1	Lacosamide	143-144

2. **Solubility**

The solubility is check in various solvents like Distilled water,DMSO , Dimethyl Fromamide, Ethanol

3. **UV- Visible Callibration of lacosamide :-**

A UV spectrophotometric procedure for analyzing lacosamide in patch involves preparing a lacosamide stock solution, preparing calibration standards,selecting a wavelength, constructing a calibration curve, and preparing a sample. 100mg lacosamide dissolve in 100ml phosphate buffer 6.8 (100ug/ml).Put out 10ml from above 100ug/ml solution and add 100ml again phospahte buffer 6.8(10ug/ml).From this 10ug/ml solution, put out 1,2,3,4,5ml and make

up the volume in 10ml of volumetric flask with same phospahte buffer solution which make solution of 1ug/ml,2ug/ml,3ug/ml,4gu/mland 5ug/ml solutions The maximum absorption wavelength (λmax) is typically around 207 nm. The sample is then prepared. The absorbance of the sample solution is measured at the λmax, and the concentration of lacosamide is determined using the calibration equation. Plot the callibration curve graph of concentratin VS absorbance.

Sr. no	Media	Solubility
1	Water	Highly soluble
2	Ethanol	Sparingly soluble
3	DMSO	Sparingly soluble
4	Dimethyl Fromamide	Sparingly soluble

4. FT-IR:-

The IR is done by using the BRUCKER IR spectrometer is a crucial method for characterizing and confirming the presence of functional groups in chemical compounds and formulations. Approximately 1–2mg of lacosamide powder, physical mixtures were placed in a mortar and then crushed until homogeneous then formed pellets with a pressure of 800 m Pa under vacuum and analyzed by Fourier-transform infrared (FTIR) spectrophotometer. Absorption spectra were recorded at wave number 500–4000 cm-1The IR spectrometer is then used to analyze the recorded spectrum to identify characteristic absorption bands lacosamide, compare it with reference spectra or literature data, and interpret the observed absorption bands in terms of structural features of lacosamide. The results of the IR spectroscopy analysis are reported, including the identified absorption bands and their assignments to specific molecular vibrations of lacosamide If necessary, differences or similarities between the experimental spectrum and reference data can be discussed.

A. EXPERIENTAL DESIGN:

Materials for patch :

Materials commonly used for the preparation of transdermal patch are summarized in Table Below

Sr No.	Materials
1	Methanol
2	Poly Ethylene Glycol
3	Propylene Glycol
4	Chloroform

Formulation of transdermal patch:

The patches were developed by solvent casting evaporation technique. HPMC K4M polymers were used. Different concentrations of polymers were added in 30 ml volume of solvent Methanol: Chloroform (3:2). The polymeric dispersion stirred with magnetic stirrer for about 10 min to form clear solution. Weighed amount of polyethylene Glycol 400 and propylene glycol was added to above solution. 5o mg of drug was mixed thoroughly by the use of magnetic stirrer for few minutes. The uniform solution was formed which was poured into petri plate and placed inverted funnel which will help to control the evaporation of solvent and will avoid the cracking of patches. This was kept aside for overnight. Dried patches were separated from the plate, cut and stored in desiccator.

Batch No.	Std	ID	Run	Build Type	Space Type	Factor A: HPMC	Factor B: PEG %	Response 1:in vivo	Response 2: tensile strength

						MG		**release %**	
F1	10	9	1	NA	Central	500	30	100	0.216
F2	7	7	2	NA	Axial	500	15.8579	192.67	0.238
F3	2	2	3	NA	Factorial	700	20	87.23	0.248
F4	6	6	4	NA	Axial	782.843	30	100	0.249
F5	5	5	5	NA	Axial	217.157	30	100	0.173
F6	13	9	6	NA	Center	500	30	100	0.216
F7	12	9	7	NA	Center	500	30	100	0.216
F8	3	3	8	NA	Factorial	300	40	91.83	0.243
F9	4	4	9	NA	Factorial	700	40	72.81	0.269
F10	8	8	10	NA	Axial	500	44.1421	94.23	0.254
F11	11	9	11	NA	Center	500	30	100	0.216
F12	1	1	12	NA	Factorial	300	20	100	0.135
F13	9	9	13	NA	Center	300	30	100	0.216

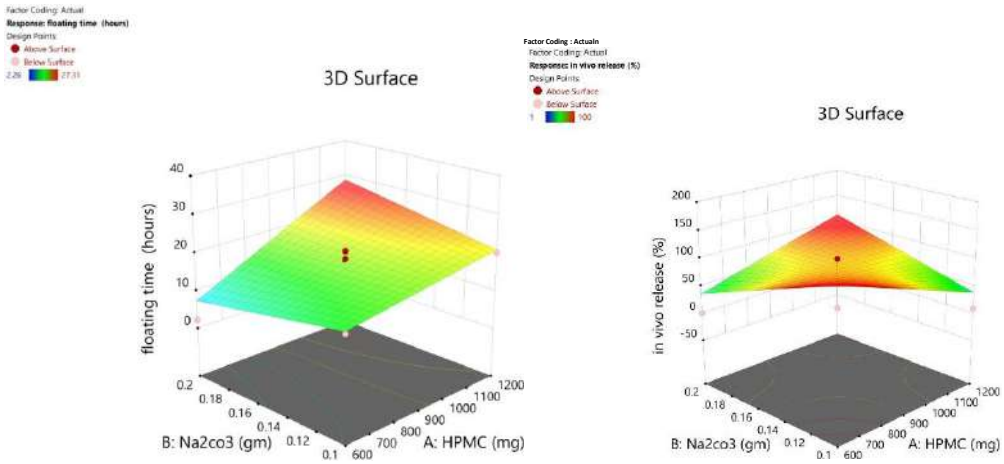


Fig 19 (A)&(B): 3D Surfce plot graph

3D Surfce morphology shows a smooth graph of tensile strength is increased with the concentration of HPMC.Each factors are normal and give smooth graph and normal interactions.It is also clear the ammount of HPMC is responsible.

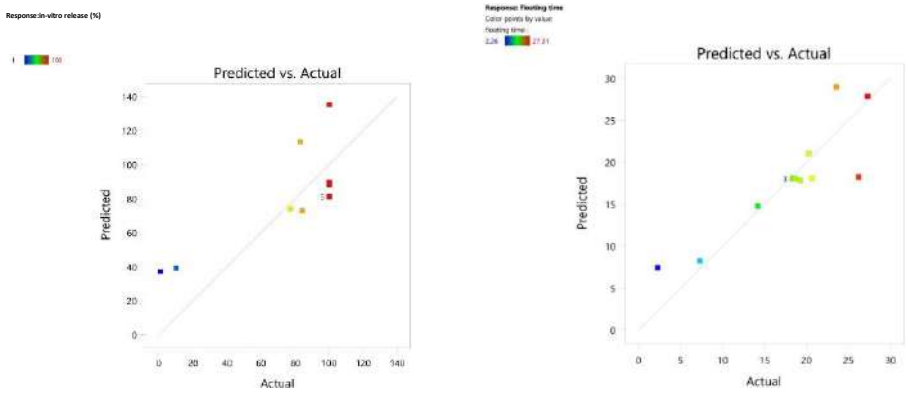


Fig 20 Predicted VS Actual Graph:(A)&(B): By observing Predicted VS actual graph, it is shows that the most of points comes near to the diagonal lines of both acutual and predicted diagonal lines so as per figure floating time on actial and model shows our models has good performance for floating time model by comparing the predicted values and in the sense of in-vitro models few points are far from diagonal

lines and few points are actual and predicted are on diagonal lines so it shows better performanec on predicted values

ANOVA for 2FI model Response 1:

Table 10 :ANOVA for 2FI model ; Response 1:

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	444.53	3	148.18	10.19	0.0030	significant
A-HPMC	386.23	1	386.23	26.56	0.0006	
B-PEG	0.1678	1	0.1678	0.0115	0.9168	
AB	58.14	1	58.14	4.00	0.0766	
Residual	130.86	9	14.54			
Lack of Fit	126.71	5	25.34	24.46	0.0043 significant	significant
Pure Error	4.14	4	1.04			
Cor Total	575.39 12					

Factor coding is Coded.

Sum of squares is Type III - Partial

The Model F-value of 10.19 implies the model is significant. There is only a 0.30%chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. The Lack of Fit F-value of 24.46 implies the Lack of Fit is significant. There is only a 0.43% chance that a Lack of Fit F-value this large could occur due to noise. Significant lack of fit is bad -- we want the model to fit.

Fit Statistics

Table 11 :Fit Statistics for floating resopne

Std. Dev.	3.81	R2	0.7726
Mean	18.05	Adjusted R2	0.6968
C.V. %	21.12	Predicted R2	0.1767
		Adeq Precision	10.1750

The Predicted R^2 of 0.1767 is not as close to the Adjusted R^2 of 0.6968 as one might normally expect; i.e. the difference is more than 0.2. This may indicate a large block effect or a possible problem with your model and/or data. Things to consider are model reduction, response transformation, outliers, etc. All empirical models should be tested by doing confirmation runs. Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable.Your ratio of 10.175 indicates an adequate signal. This model can be used to navigate the design space.

Model Comparison Statistics

Table 12 :Model Comparison Statistics for floating resopne

PRESS	473.74
-2 Log Likelihood	66.91
BIC	77.17
AICc	79.91

Coefficients in Terms of Coded Factors

Table 13 :Coefficients in Terms of Coded Factors for floating resopne

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	18.05	1	1.06	15.66	20.44	
A-HPMC	6.95	1	1.35	3.90	10.00	1.0000
B- PEG	0.1448	1	1.35	-2.90	3.19	1.0000
AB	3.81	1	1.91	-0.5004	8.13	1.0000

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-colinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.

Final Equation in Terms of Coded Factors

floating time =
+18.05
+6.95 A
+0.1448 B
+3.81 AB

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparision

ANOVA for 2FI model Response 2: in vitro release

Source	Sum of Squares	df	Mean Square	F-value	p-value
Model	7906.94	3	2635.65	3.68	0.0561
A-HPMC	199.32	1	199.32	0.2781	0.6107
B-Na2co3	288.39	1	288.39	0.4023	0.5417
AB	7419.24	1	7419.24	10.35	0.0105
Residual	6451.28	9	716.81	nan	Nan
Lack of Fit	6451.28	5	1290.26	nan	Nan
Pure Error	0.0	4	0.0	nan	Nan
Cor Total	14358.23	12	nan	nan	Nan

Factor coding is Coded.

Sum of squares is Type III - Partial

The Model F-value of 3.68 implies there is a 5.61% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case AB is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Fit Statistics

Table 15 : Fit Statistics for in-vitro release

Std. Dev	26.77	R^2	0.5507
Mean	81.21	Adjusted R^2	0.4009
C.V.%	32.97	Predicted R^2	-0.8768
		Adeq	6.6084

		Precision	

A negative Predicted R^2 implies that the overall mean may be a better predictor of your response than the current model. In some cases, a higher order model may also predict better. Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable.Your ratio of 6.608 indicates an adequate signal. This model can be used to navigate the design space.

Model Comparison Statistics

Table 16 :Model Comparison Statistics in vitro release

Statistic	Value
PRESS	26947.89
-2 Log Likelihood	117.58

Coefficients in Terms of Coded Factors in vitro release

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF	Factor
Intercept	81.21	1	7.43	64.41	98.01	nan	Intercept
A-HPMC	-4.99	1	9.47	-26.4	16.42	1.0	A-HPMC
B-Na2co3	-6.0	1	9.47	-27.42	15.41	1.0	B-Na2co3
AB	43.07	1	13.39	12.78	73.35	1.0	AB

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-colinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.

Final Equation in Terms of Actual Factors

in vivo release =

+501.80392

-0.447313 HPMC

-2704.13037 PEG

+2.87117 HPMC * PEG

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

Coefficients in Terms of Coded Factors

Final Equation in Terms of Actual Factors

in vivo release =

+501.80392

-0.447313 HPMC

-2704.13037 PEG

+2.87117 HPMC * PEG

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

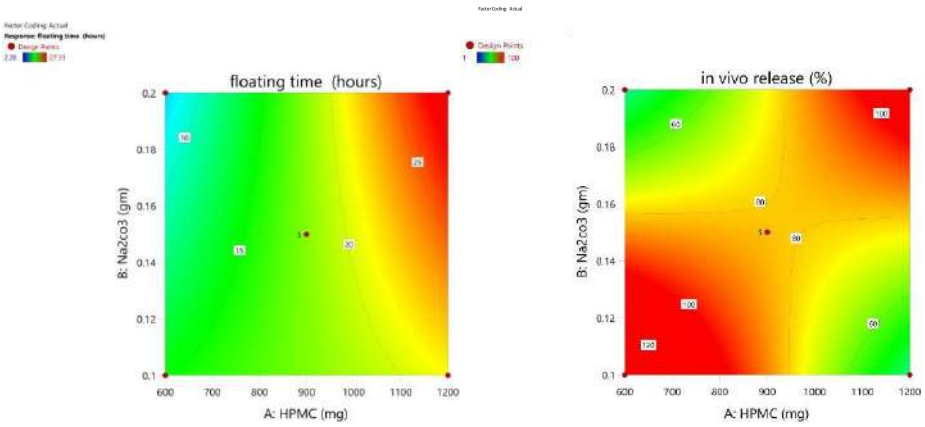


Fig21:(A) **Fig21:(B)**

Fig 21 (A): The counter plot shows that a good grid on floating time for on x-axis HPMC and y-axis PEG The counter plot shows that interpolation results and increases in concentration of PEG i.e.Y-axis is increasing the tensile strength The effect of HPMC is slightly affected.

Fig 21(B): The Counter plot indicates that it is affected by the concentration of HPMC i.e.variables of X-axis and the Y-axis of PEG i.e variable on Y-axis does not affect the in-vitro relase.

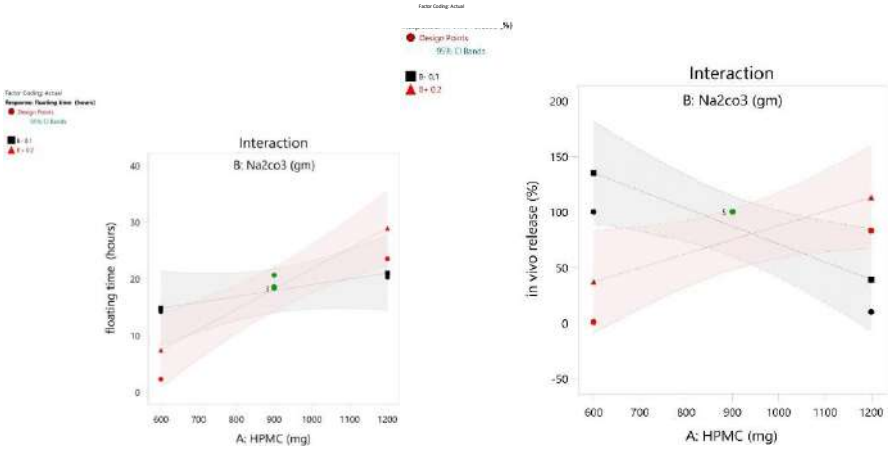


Fig 22: (A) **Fig21:(B)**

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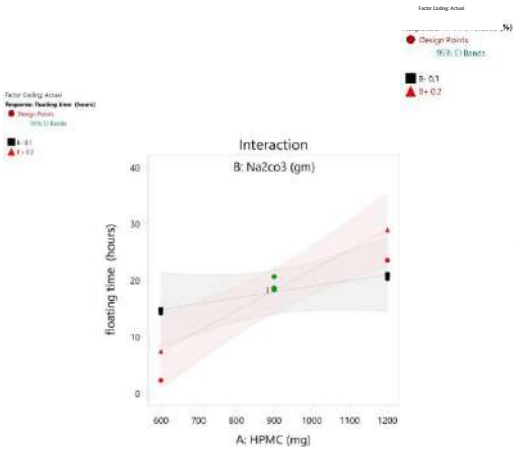


Fig 22: (A)

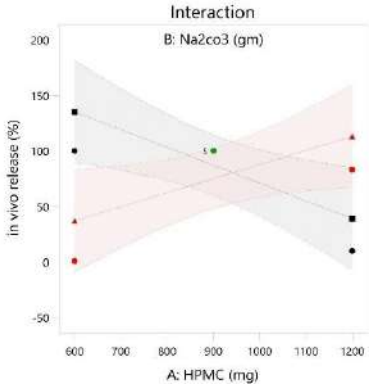


Fig22 :(B)

Fig 22 (A)&(B): The interaction graph of both floating and in vitro the lines of both the variables are crossing to each others and it shows the interactions of variables with each other. It shows the concentration of each variables are affect to each others.

Desirabilility

Constraints

Solutions

100 Solutions found

Table 19 : Floating resopnse Desirabilility:Solutions

Sr. No	HPMC	PEG	TENSILE STRENGTH	StdErr(floating time)	in vivo release	StdErr(in vivo release)	Desirability	
1	1140.768	0.184	25.783	2.042	96.406	14.336	1.000	Selected
2	600.00	0.100	25.783	2.042	96.406	14.336	1.000	
3	600.00	0.200	14.772	2.896	135.273	20.336	1.000	
4	1200.000	0.100	7.436	2.896	37.130	20.336	1.000	
5	1200.000	0.200	21.043	2.896	39.155	20.336	1.000	
6	812.163	0.178	28.958	2.896	113.282	20.336	1.000	
7	1174.191	0.193	15.468	1.399	72.125	9.824	1.000	
8	1184.494	0.124	27.540	2.503	105.486	17.574	1.000	
9	790.276	0.118	22.684	2.032	58.346	14.270	1.000	
10	868.309	0.166	16.302	1.512	96.810	10.614	1.000	
11	869.735	0.130	17.234	1.156	78.292	8.118	1.000	
12	863.188	0.160	17.448	1.199	85.888	8.422	1.000	
13	812.864	0.181	17.137	1.103	79.634	7.743	1.000	
14	847.784	0.125	15.433	1.449	71.102	10.174	1.000	
15	784.178	0.199	17.107	1.294	88.963	9.087	1.000	
16	727.635	0.196	14.075	1.907	61.052	13.389	1.000	
17	766.944	0.133	12.169	2.073	55.654	14.555	1.000	
18	884.346	0.103	15.492	1.328	91.887	9.325	1.000	
19	650.771	0.122	17.740	1.652	89.202	11.597	1.000	
20	1126.682	0.171	14.000	1.943	109.137	13.640	1.000	
21	972.053	0.199	24.588	1.691	88.712	11.871	1.000	
22	892.411	0.133	20.770	1.790	84.302	12.569	1.000	
23	673.075	0.104	17.860	1.153	83.741	8.094	1.000	
24	1079.340	0.185	15.341	2.350	120.824	16.498	1.000	

25	808.434	0.144	23.903	1.815	92.047	12.746	1.000	
26	795.798	0.183	16.052	1.148	85.006	8.061	1.000	
27	1100.629	0.177	14.856	1.527	69.033	10.720	1.000	
28	1177.551	0.112	24.171	1.720	90.323	12.077	1.000	
29	1148.830	0.108	21.712	2.340	51.076	16.431	1.000	
30	1189.117	0.165	21.024	2.333	51.986	16.384	1.000	
31	757.600	0.184	25.896	1.810	87.064	12.707	1.000	
70	898.060	0.160	18.032	1.094	79.936	7.682	1.000	
71	990.726	0.178	20.870	1.393	83.578	9.781	1.000	1
72	900.482	0.109	17.940	1.529	86.066	10.739	1.000	
73	1167.018	0.136	23.271	1.705	67.940	11.974	1.000	
74	879.992	0.138	17.615	1.111	83.686	7.798	1.000	
75	1099.542	0.179	24.246	1.761	91.172	12.365	1.000	
76	736.096	0.156	14.024	1.305	80.403	9.162	1.000	
77	606.041	0.111	14.042	2.467	123.666	17.323	1.000	
78	1024.698	0.184	22.104	1.593	87.139	11.189	1.000	
79	732.101	0.178	13.036	1.624	66.928	11.405	1.000	
80	706.972	0.179	12.252	1.724	65.001	12.107	1.000	
81	913.903	0.177	18.547	1.284	78.829	9.013	1.000	
82	1122.479	0.199	26.117	2.405	102.918	16.883	1.000	
83	660.804	0.187	10.390	2.120	55.614	14.882	1.000	
84	980.836	0.188	20.819	1.569	84.139	11.018	1.000	
85	968.408	0.160	19.843	1.138	80.848	7.993	1.000	
86	676.135	0.139	13.440	1.518	93.029	10.657	1.000	
87	605.063	0.186	8.594	2.390	50.862	16.778	1.000	
88	678.478	0.190	10.782	2.133	54.610	14.973	1.000	
89	901.212	0.194	18.220	1.583	76.095	11.116	1.000	
90	705.914	0.159	13.145	1.409	78.428	9.891	1.000	
91	609.683	0.159	10.690	1.729	77.457	12.140	1.000	
92	1164.068	0.146	23.910	1.597	74.463	11.216	1.000	
93	730.931	0.118	15.417	1.706	103.372	11.977	1.000	
94	867.497	0.196	17.055	1.639	72.027	11.505	1.000	
95	913.829	0.103	18.070	1.657	84.771	11.637	1.000	
96	763.841	0.129	15.561	1.393	94.151	9.782	1.000	
97	823.975	0.107	16.994	1.654	96.950	11.615	1.000	
98	1056.360	0.145	21.476	1.279	77.083	8.982	1.000	
99	1014.553	0.174	21.459	1.380	84.217	9.687	1.000	
100	909.189	0.166	18.349	1.143	79.555	8.028	1.000	

EVALUATION

Organoleptic characteristics of drug substances

Organoleptic Identification: The drug samples were physically identified i.e. Color, odor and taste etc.

Sr.no	Drug	Color	Odor	Taste
1.	Lcosamide	White	Odorless	Testless

Thickness:

Screw gauze was used for the determination of thickness of 10 selected patches. Thickness was measured at 5 different locations. And average was calculated (Mounika et al., 2014).

Uniformity of weight:

Uniformity of weight was calculated by weighing the patches on digital balance. The test was performed on 5 patches and average weight was calculated (Mounika et al., 2014).

Moisture content:

For moisture content, desiccator with fused calcium chloride was used. Patches to be evaluated were initially weighed and put in a desiccator for 24 h. After 24 h patches were reweighed and moisture content was calculated by subtracting the final weight from initial weight with respect to initial weight (Mounika et al., 2014).

Folding endurance

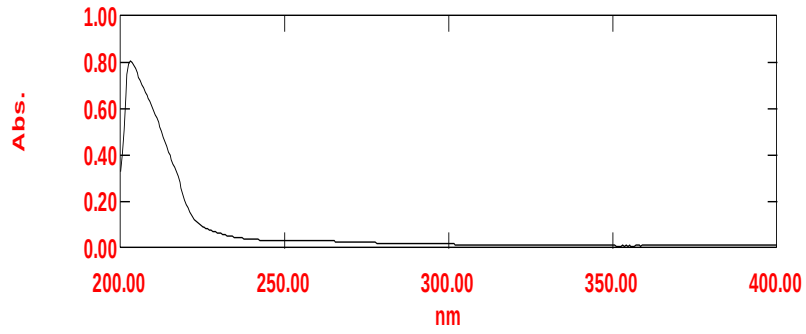
Folding endurance was determined by folding the patch several numbers of time at same time and at same place till patch broke.The number at which patch fold without breaking will give the value of folding endurance (Mounika et al., 2014).

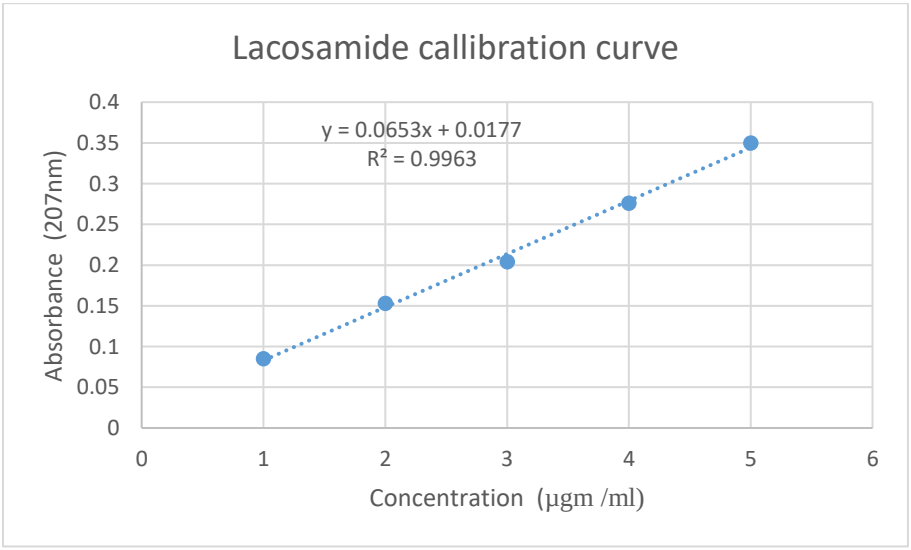
Skin irritation test:

Skin irritation test was done to check that the formulation is free from any skin irritation.

Preparation of calibration curves of Lacosamide By UV at λmax 206 nm.

Sr. No	Concentration (µgm/ml)	AUC (207nm)
1	0	0
2	1	0.0850
3	2	0.153
4	3	0.204
5	4	0.2769
6	5	0.350
r^2	0.9963	





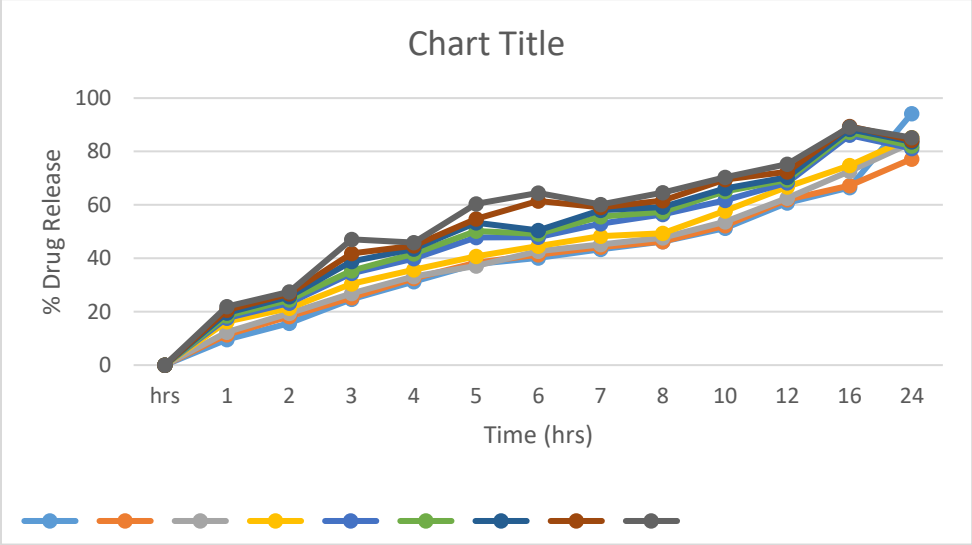
phosphate buffer solution (PBS) 7.4 ph, magnetic stirrer, analytical balance, syringe, sampling vials, and a UV-Vis spectrophotometer for drug quantification. The membrane is prepared by removing any subcutaneous fat and hydrating it in PBS for at least an hour before the experiment. The Franz diffusion cell is assembled, consisting of a donor compartment and a receptor compartment, filled with PBS and maintained at a constant temperature. A magnetic stirrer is placed in the receptor compartment to ensure uniform drug distribution

Fig no In vitro drug release

The transdiffusion procedure for benzocaine transferosome gel involves evaluating drug permeation through a biological membrane using various tools. The membrane is prepared, Franz diffusion cells are assembled,and a magneti stirrer is placed in the receptor compartment.

Time interval	Drug release (%)
0	0
30	0.1022
60	0.4286
90	0.4716
120	0.5039
150	0.6346
180	0.7511
210	0.8553
240	0.9766
270	100

32.44	33.21	35.67	39.89	41.67	43.56	44.66	45.92
38.33	37.14	40.77	47.77	50.23	53.33	54.81	60.41
41.33	42.65	44.55	47.88	49.11	50.43	61.45	64.43
44.28	45.23	48.34	52.99	55.56	57.98	59.13	60.12
46.23	47.67	49.33	56.44	57.42	59.23	61.57	64.56
52.3	53.67	57.78	61.77	65.13	66.12	69.54	70.34
61.98	62.56	66.78	68.33	69.43	70.32	72.44	75.22
67.28	72.67	74.78	86.12	87.22	88.34	89.44	89.11
77.23	83.33	85.23	81.11	82.11	83.66	84.22	85.23



FT-IR:-

a. Drug FTIR-

Approximately 1–2mg of Lacosamide powder, physical mixtures were placed in a mortar and then crushed until homogeneous then formed pellets with a pressure of 800 mPa under vacuum and analyzed by Fourier-transform infrared (FTIR) spectrophotometer. Absorption spectra were recorded at wave number 500–4000 cm-1 .

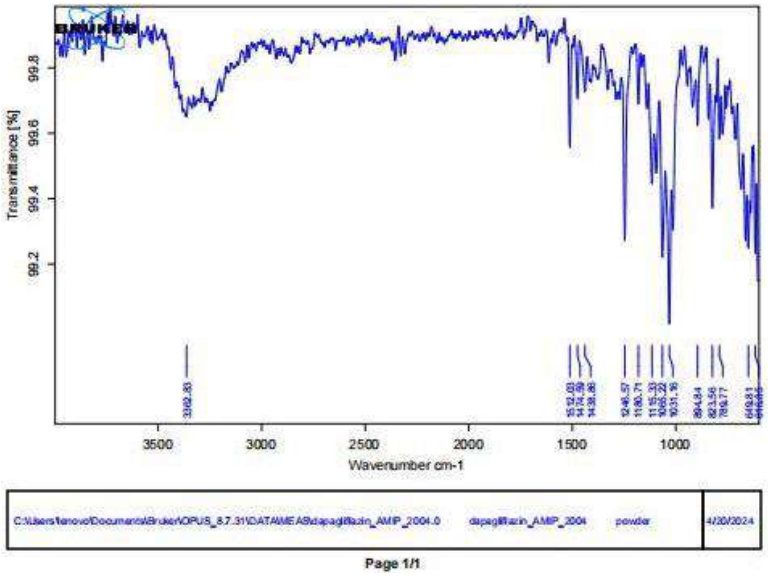


Table 24 :Functional groups present in drug FTIR

Functional Group	Stretching peak range (cm^{-1})	Observed peak range (cm^{-1})
C-H	Stretching	
Aliphatic	-	-
N-H Stretching	3500-3200	
N-H Bending	1800-2500	
SO2NH Stretching	1600-1300	
C=O Stretching	2000-1700	

S=O Stretching	1400-1100	

b. Drug And Polymer FTIR

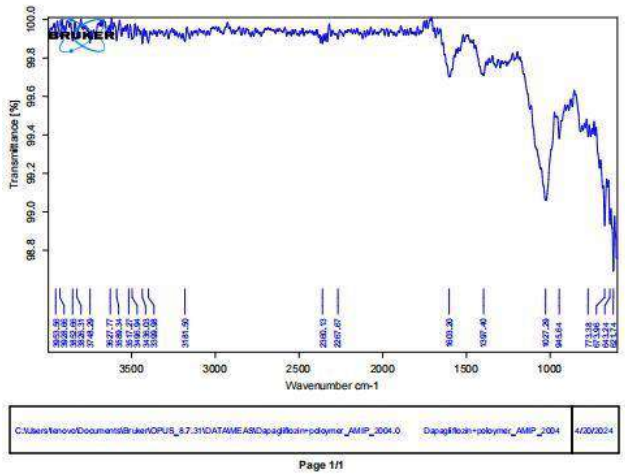


Fig 30 :Drug with FTIR

SUMMARY AND CONCLUSION

A new controlled release system of transdermal patch were formulated by an solvent evaporation method using central composite design technique of design of experiments. The current study aimed to develop and optimize control release patch in order to prolong the residence time of drug on gastric region, thereby, improving their solubility and bioavailability. The effect of amounts as independent process variables on the properties or response of these newly developed beads containing lacosamide like drug encapsulating and drug release were optimized. The in-vitro drug release from this beads followed first orderand evaluated. This properties of newly developed beads could possibly advantageous in term of advanced patient compliance with reduced dose interval

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