Annals of Case Reports and Clinical Studies

Research Article (ISSN: 2834-5673)

Formulation and Evaluation of Press Coated Tablets of Duloxetine HCl Using Hydroxy Propyl Methyl Cellulose Pthalate in Odrer to Release the Drug in the Intestine

Lakshmi Savithri S, Thangabalan B, Jasmine SK*, Nandini Y, Jahnavi P, Tanuja M, Pradeep Chopra G, Karthik B, Vamsi K

Department of Pharmaceutics, SIMS College of Pharmacy, India

Citation: *Lakshmi Savithri S, Thangabalan B, Jasmine SK, Nandini Y, Jahnavi P, Tanuja M, et al. Formulation and Evaluation of Press Coated Tablets of Duloxetine HCl Using Hydroxy Propyl Methyl Cellulose Pthalate in Odrer to Release the Drug in the Intestine. Ann Case Rep Clin Stud. 2023;2(2):1-46.*

Received Date: 18 March, 2023; **Accepted Date:** 24 March, 2023; **Published Date:** 26 March, 2023

***Corresponding author:** Jasmine SK, Department of Pharmaceutics, SIMS College of Pharmacy, India

Copyright: © Jasmine SK, Open Access 2023. This article, published in Ann Case Rep Clin Stud (ACRCS) (Attribution 4.0 International), as described by http:// creativecommons.org/licenses/by/4.0/.

ABSTRACT

Oral drug delivery is the method of swallowing a pharmaceutical compound with the intention of releasing it into the gastro intestinal tract of humans and animals the purpose of Duloxetine HCL Press coated tablets were created with intention of delaying drug release to enable release in the lower region of the gastro intestinal tract. The other excipients like diet basic calcium phosphate , magnesium stearate , talc and different concentration of super disintegrates The like sodium starch , glycolate formulation of {F44 and F45} were developed to sustained the drug release from the tablet dosage form the drug release of formulations F44 and F45 was found more than 75% of drug with in 45mins in a basic medium so the combination of 60% of HPMCP and 6% sodium starch glycolate was best for the enteric coating which has given hardness, friability, weight variation, content uniformity , % drug release and disintegration and dissolution with in officially specified limits immediate release of tablet of duloxetine HCL as promising approach of enhance the drug release profile using combination of super disintegrant the results showed that from above dissolution study the formulation F44 and F45 give 98.9% drug in 60mins and also showed good hardness, thickness, friability, disintegration time, so it is selected as optimized formulation so immediate release tablet of duloxetine HCL shows better release profile as compared to other formulation . Finally, the tablet was press coated together.

Keywords: Duloxetine HCL, HPMC, HPMCP, Calcium phosphate, sodium disintegrates, Press coated tablets, Immediate release.

Research Article (ISSN: 2834-5673)

AIM AND OBJECTIVE:

Aim

The aim of present work is to formulate and evaluate press coated tablets of DULOXETINE HCL (DLX) using Hydroxypropyl methylcellulose (HPMCP) Phthalate in order to release the drug in the intestine.

Experimental Objective

To design & evaluate Press coated tablet of DLX will formulate with an aim to prevent to gastric degradation of the drug so as to improve the bioavailability of the drug.

- Selection of drug candidate.
- For peripheral neuropathy: Duloxetine Hydrochloride.
- For diabetes: Metformin.
- Pre-formulation studies of duloxetine.

(a) Identification studies (physical state, Melting point, IR spectra etc...,)

(b) Solubility studies (Solubility of drug in different solvents and buffers).

(c) Calibration curve (Drug estimation methods)

(d) In vitro dissolution method development.

(e) Compatibility studies (Drug-polymer reactions)

(f) Micrometric properties, etc.,

- Selection polymer.
- To prevent gastric degradation of Duloxetine Hydrochloride – HPMCP.
- To show immediate release action of Metformin and Duloxetine Hydrochloride – Sodium starch glycolate (SSG).
- Formulation of core tablets (Duloxetine Hydrochloride)
- Evaluation of core tablets.
- Formulation of press coated tablet (HPMCP).
- Evaluation of press coated tablets.
- Formulation of encoated tablet layer (Metformin).
- Evaluation of encoated tablet layer.

INTRODUCTION

Oral Drug Delivery System

Oral drug delivery is the method of swallowing a pharmaceutical compound with the intention of releasing it into the gastrointestinal tract of humans and animals. The gastrointestinal tract comprises the mouth, stomach, small bowel and large bowel. The oral delivery method is the most agreeable among the delivery methods in terms of patient compliance. Many pharmaceutical companies have focused their research efforts on creating novel dosage

Research Article (ISSN: 2834-5673)

formulations for previously prescribed medications. A perfect medicine delivery system offers patients long-term treatment for acute or chronic illness. There are several oral dose formulations available**.** The majority of them are solids, although some are liquids (such as syrups, elixirs, tinctures, suspensions, and emulsions) (e.g., tablets and capsules). To speed up systemic absorption, tablets and capsules are typically designed to release the medication right away after oral administration; they are known as immediate-release medicines. To release the medication at a controlled rate, other products such as modified release dosage form have been created.

Compression Coated Tablets

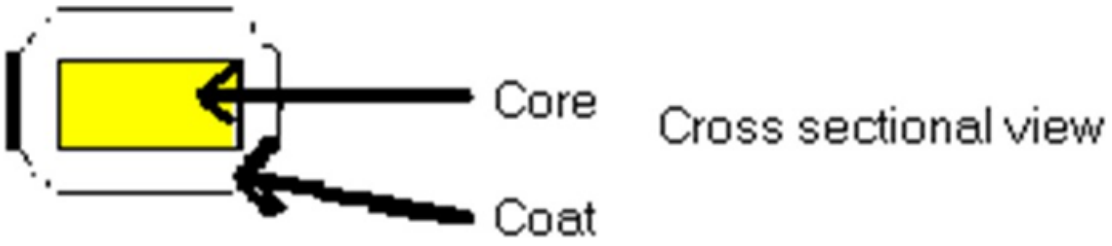


Figure1. Compression coated tablets

Table.1 Types of tablets

Oral tablets for ingestion: These tablets are meant t swallowed intact along with a sufficient quantity potable water. The exception is a chewable tablet. 90% of the tablets manufactured today are ingested or This shows that this class of formulation is the popular worldwide and the major attention of researcher is towards this direction.	□ Standard compressed tablets □ Multiple compressed tablets o ǫ Compression coated tablets ǫ Layered tablet Inlay tablet □ Modified Release tablet Delayed □ action tablet Targeted tablet □ Floating tablet □ Colon targeting tablet Chewable □ tablet Dispersible tablet □ □
Tablets used in the oral cavity: The tablets under group are aimed release API in the oral cavity o provide local action in this region. The tablets under category avoid the first-pass metabolism, decomposition in gastric environment, nauseatic sensations and g rapid onset of action. The tablets formulated for region are designed to fit in proper region of the cavity.	➢ Lozenges and troches ➢ Sublingual tablet ➢ Buccal tablet ➢ Dental cones ➢ Mouth dissolved tablet
Tablets administered by other routes: These tablet administered by another route except for the oral ca and so the drugs are avoided from passing through gastrointestinal tract. These tablets may be inserted other body cavities or directly placed below the skin t absorbed into the systemic circulation from the sit application.	➢ Vaginal tablet ➢ Implants

Tablets used to prepare solution: The tablets under category are required to be dissolved first in water other solvents before administration or application. solution may be for ingestion or parenteral application for topical use depending upon the type of medica used.	➢ Effervescent tablet ➢ Hypodermic tablet ➢ Soluble tablet

Diabetic Neurotherapy

Damage to the nerves that allow you to sense things like pain is known as diabetic neuropathy, a common complication of diabetes. Diabetes can harm nerves in a number of ways, but they all appear to be linked to prolonged periods of high blood sugar. Diabetes affects 347 million individuals globally. An estimated 1.5 million cases of diabetes were directly responsible for these cases in 2012. 50% of people with diabetes also have an increased chance of developing heart disease. The most prevalent neuropath in the West is diabetic polyneuropathy. Depending on the diagnostic criteria and Pati populations analyzed, it has been projected that 10 to 100% of diabetic patients may develop clinical and subclinical neuropathy. Diabetes neuropathy is divided into several clinical syndromes a collection of traits.

Distal symmetric polyneuropathy.

- Autonomic neuropathy.
- Thoracic and lumbar nerve root disease, causing polyradiculopathies.
- Individua cranial and peripheral nerve involvement causing focal mononeuropathies, especially affecting the oculomotor nerve (cranial nerve III) and median nerve.
- Asymmetric involvement of multiple peripheral nerves, resultingin mononeuropathy multiplex.

Treatment Of Diabetic Neurpathy

The treatment of diabetic peripheral neuropathy will be reviewed here. There are three main elements in the treatment regimen:

- Glycemic control
- Foot care
- Treatment of pain

Glycemic Control For Established Neuropathy

At least in patients with type 1 diabetes mellitus, optimal glucose control is crucial for the prevention of diabetic neuropathy. Glucose management helped type 1 patients in the major Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) trial delay the onset of neuropathy and slow the advancement of substitute electrophysiologic indicators of neuropathy. According to a 2005 practice statement from the American Diabetes Association, individuals with symptomatic diabetic polyneuropathy should initially strive for stable and ideal glucose control. In a 2012 systematic review, increased glucose was found to be

associated with statistically significant improvements in surrogate measures of neuropathy, such as nerve conduction velocity and vibration perception thresholds. These data support the possibility of symptomatic improvement. In addition, clinical experience suggests that vigorous glycemic control is associated with improvement in symptoms for patients who develop acute painful diabetic neuropathy after a period of extreme hyperglycemia such as diabetic ketoacidosis. Nevertheless, established symptomatic diabetic neuropathy is generally not reversible even with intensive glucose control, emphasizing the importance of prevention. Results from a small observational trial raise the possibility, but do not show, that gastric bypass surgery for obese people with type 2 diabetes can improve glycemic control and diabetic neuropathy symptoms temporarily. To ascertain whether this strategy benefits patients with type 2 diabetes and neuropathy caused by obesity over the long run, larger and more thorough trials are required.

Foot Care

We integrate foot care with effective glycemic management. Patients must regularly examine their feet for dry, cracked skin, fissures, the development of a plantar callus, and early infection symptoms between the toes and around the toenails. The treatment of diabetic patients must also include routine foot inspections by the doctor to identify early neuropathy.

When a patient develops diabetic neuropathy, proper foot care becomes even more crucial in order to avoid ulceration, infection, and amputation.

Painful Diabetic Neuropathy

Patients with diabetic polyneuropathy rarely have unpleasant sensations. Individuals who have painful diabetic neuropathy should be managed in a methodical, progressive manner. Verify sure the discomfort is caused by neuropathy before beginning treatment. Here, the diagnosis of diabetic polyneuropathy is briefly reviewed and covered in-depth separately. It can be extremely upsetting and incapacitating when significant pain in the lower limbs and feet first appears. If the pain has recently been subjected to trauma or if it has a rapid beginning, a disc lesion should be taken into account. Moreover, compared to pain brought on by peripheral neuropathy, disc disease-related pain is more frequently unilateral.

The differential diagnosis in the absence of these signs is peripheral vascular disease or neuropathy. Decreased feeling or lack of deep tendon reflexes discovered during a physical examination may be beneficial, but they do not prove that the pain is caused by neuropathy. Location of the pain (foot greater than calf), nature of the pain, and timing of the pain are a few indicators that the patient has neuropathic pain (present at rest, improves with walking). Each of these characteristics is distinct from the discomfort caused by ischemic vascular disease. Acute painful diabetic neuropathy syndromes come in a variety of forms, some of which are more common than symmetric diabetic polyneuropathy. These are:

Diabetes neuropathy brought on by treatment that manifests during a period of rapid glycemic control.

Diabetic neuropathy that causes unintentional, drastic weight loss (diabetic neuropathic cachexia).

Diabetic neuropathy linked to deliberate weight loss (diabetic anorexia). These disorders typically have a possibly reversible course that can extend for many months, severe neuropathic pain, and autonomic dysfunction. Ultimately,

patients with type 2 diabetes mellitus frequently get diabetic amyotrophy. The classic symptoms are a sudden, asymmetrical, focal onset of pain, followed by proximal leg weakness, autonomic failure, and weight loss. Most patients see progression over several months, which is followed by a partial recovery.

Spontaneous Resolution

Once painful diabetic polyneuropathy has been diagnosed, the patient should be made aware of the possibility of self-limitation. For instance, 16 out of 29 patients in a prospective study had pain relief within a year (55 percent). Remission was more likely if the start of symptoms had been preceded by a significant loss of weight, a brief episode of diabetic ketoacidosis, or occasionally an improvement in glycemic control. Mechanisms may include altered perception of pain, more nerve degradation until it ceases to react to stimulation (putting the patient at much greater risk for trauma), or improved nerve function. For instance, a neuron may uncontrollably fire while being destroyed or while it is recuperating, resulting in pain. Hence, in a patient with poor glycemic control, the nerves may go without nutrition, resulting in an acute but treatable nerve damage. Yet, a previously quiet (anesthetic) nerve may now become active better glycemic control, resulting in spontaneous firing and the experience of discomfort.

Pain Control

Many antidepressants (such as amitriptyline, duloxetine, and venlafaxine), anticonvulsants (such as pregabalin and sodium valproate), and capsaicin cream are effective treatments for painful diabetic neuropathy. Alpha-lipoic acid, isosorbide dinitrate topical spray, and transcutaneous electrical nerve stimulation are some more treatments that could be helpful. The recommendations of the guidelines and our method of treatment are reviewed in the sections that follow, together with the supporting data for these interventions.

Antidepressants — Randomized controlled experiments have shown that tricyclic
medications (mostly amitriptyline) as well as the antidepressants duloxetine and venlafaxine are helpful in lowering diabetic neuropathy discomfort.

Tricyclic Drugs

Several tricyclic antidepressant drugs (but not selective serotonin reuptake inhibitors) have been found in double-blind, randomized controlled trails to improve symptoms in patients with painful diabetic neuropathy. Tricyclics may act by altering the central perception of pain. The therapeutic effect usually occurs sooner (within six weeks) and at lower doses than is typical when these drugs are given for the treatment of depression.

These points are illustrated by the following trails:

In a placebo-controlled, double-blind, randomized cross-over trail, amitriptyline and desipramine were equally effective and superior or placebo. The benefit of the tricyclic drugs was noted within two weeks and continued to increase at six weeks Desipramine had somewhat fewer side effects than amitriptyline, particularly dry mouth. The average effective dose, titrated over six weeks to achieve control of symptoms, was 111mg/day for desipramine and 105mg/day for amitriptyline. There was no correlation between relief of pain, dosage, or plasma drug concentrations, suggesting that the clinical response and tolerability of side effects are best guides to dose titration. Amitriptyline and duloxetine both significantly reduced pain as compared to pretreatment baseline in a randomized, blinded cross-over trial including 58 persons with severe diabetic neuropathy. Amitriptyline and duloxetine were

both reported to have a similar rate of favorable outcomes (defined as a median pain score reduction of >50%), and the difference between the two was not statistically significant. Amitriptyline significantly increased the frequency of dry mouth compared to duloxetine (55 versus 24%), whereas duloxetine did not significantly increase the frequency of constipation (37 versus 17 percent). Patients with significant pain receive either amitriptyline or desipramine. This class of drugs can be added to pregabalin or anticonvulsants but not to duloxetine. The starting dose of desipramine is 25mg, taken at bedtime. The dose can be increased to a maximum of 200mg/day over a few weeks.

The choice of a specific drug may vary:

If anticholinergic side effects are an issue, we usually switch amitriptyline for nortriptyline.

•Nortriptyline is a first-line medication for some professionals since it has less anticholinergic side effects than amitriptyline.

• Those with heart problems should not use amitriptyline or nortriptyline. The least cardiotoxic tricyclic antidepressant medication, such as duloxetine or venlafaxine, or doxepin are given to these individuals after consulting with their cardiologist.

Dry mouth and somnolence are typical adverse effects of tricyclic antidepressants. With a dosage before bed, we advise starting tricyclic therapy. Particularly in males with enlarged prostates, urinary retention is possible.

Venlafaxine

Extended-release (ER) venlafaxine was tested in a randomized controlled experiment on 244 patients with painful diabetic neuropathy. In comparison to placebo, ER venlafaxine treatment was linked with a substantial improvement in the key end measures of pain intensity and pain alleviation after six weeks, but not at lower dosages (75 mg daily). The short length of this trial limits the strength of this finding. The most frequent side effects of venlafaxine were nausea and somnolence, while blood pressure and heart rhythm alterations happened more frequently with venlafaxine treatment than with placebo.

Anticonvulsants

Both newer (pregabalin) and older (valproate) anticonvulsants may be useful for treating painful diabetic polyneuropathy (DPN). The utility of gabapentin is uncertain.

Pregabalin

Pregabalin is a structurally related alpha2-delta ligand to gabapentin but has no known GABA or benzodiazepine receptor action. The release of excitatory neurotransmitters including glutamate, substance P, and calcitonin gene-related peptide appears to be inhibited presynaptically by it (CGRP).

Using a total of 1510 patients in the intention-to-treat population, a pooled analysis of seven randomized clinical trials with a duration of 5 to 13 weeks examined the efficacy of pregabalin for the treatment of painful diabetic neuropathy.

The following observations were reported:

• Pregabalin treatment at total daily dosages of 150, 300, and 600 mg decreased mean pain score, the main outcome of all included studies, statistically significantly when compared with placebo. Pregabalin (at 150mg, 300mg, and

Research Article (ISSN: 2834-5673)

600mg) and the placebo required, respectively, 13,5,4 and 60 days to achieve a sustained 1 point improvement on an 11-point pain score.

• There was a definite dose-related improvement in efficacy and an increase in the frequency of the majority of side events with higher dosages. Dizziness, sleepiness, and peripheral edema were the most typical side effects. Pregabalin patients were considerably more likely than placebo patients to experience clinically meaningful weight gain (defined as a percent increase in weight from baseline to end point) (2.0 to 3.9 percent versus 0.7 percent), but weight gain had no impact on diabetes control.

• Over the course of a week or more, the maximum dose of pregabalin allowed by the FDA for diabetes-related neuropathic pain is gradually increased from 50 mg twice daily (totaling 100 mg/day) to 150 mg twice daily (totaling 300 mg/day). Furthermore, 100 mg can be given three times day. Pregabalin has a multitude of adverse effects, including drowsiness, vertigo, ataxia, diplopia, blurred vision, disorientation, and sleepiness. It is a Category V substance in the United States and has the potential to establish habits. There is a general consensus that greater clinical testing of the medicine will demonstrate that its benefit surpasses any potential for habit formation.

Gabapentin

The usefulness of gabapentin in treating uncomfortable diabetic neuropathy is debatable.

In a systematic review, with data from six trials and 1277 participants, the

proportion of patients achieving, at least, a 50 percent pain intensity reduction was significantly higher with gabapentin (dosed at ≥1200 mg daily) compared with placebo (38 versus 21 percent, relative risk 1.9, 95% CI 1.5-2.3). All of the evidence was considered " the second tier" with potentially important residual biases.

A study of published and unpublished trials questioned the efficacy of gabapentin, and there are unpublished randomized controlled trials examining gabapentin for the treatment of painful diabetic neuropathy that have generated serious concerns that it is not more effective than placebo.

Given that the available evidence is incomplete, the role of gabapentin in the treatment of painful diabetic neuropathy is controversial. Some experts no longer use gabapentin for painful diabetic neuropathy, believing it to be no better than placebo. However, the clinical experience of other experts and the published data from randomized trials suggest that gabapentin has a role.

Typical starting doses for gabapentin are 300 to 600 mg three times daily; the drug can be titrated slowly up to 900 mg four times daily. The major side effects of gabapentin are somnolence, dizziness, and ataxia.

Other Convulsants

In two small, single-center placebo-controlled trials, valproic acid (500–1200 mg daily) proved beneficial in lowering pain in diabetic neuropathy. For women who are or may become pregnant, it should not be used to treat diabetic neuropathy due to teratogenic consequences. For the treatment of painful diabetic neuropathy, carbamazepine may also be helpful, however this has not been examined in recent randomized trials neuropathy. Topiramate is not helpful for excruciating diabetic polyneuropathy, according to a systematic analysis that examined data from three randomized studies.

Research Article (ISSN: 2834-5673)

Capsaicin Cream

Several spicy peppers naturally contain the compound capsaicin, which reduces substance P locally to produce analgesia. It is offered as a cream for topical use. Capsaicin has been shown to significantly reduce pain in comparison to placebo in randomized studies of people with painful diabetic neuropathy. For patients with symptomatic painful diabetic polyneuropathy who are refractory to or intolerable of the antidepressants (e.g., amitriptyline, duloxetine, venlafaxine) or anticonvulsants (e.g., pregabalin) mentioned above, we add capsaicin (0.075 percent applied topically four times daily). The possibility of local burning and skin irritation decreases with repeated application. The local burning discomfort, which is made worse by contact with warm water and hot weather, is however intolerable for many people.

Anesthetic Drugs

A 2011 systematic review found that there is inconsistent evidence about mexiletine's efficacy. The highest-quality trial considered demonstrated no discernible advantage for mexiletine over a placebo. Several studies, however, suggested a benefit.

An open-label experiment that involved 56 patients with severe diabetic neuropathy discovered that using up to four lidocaine patches for up to 18 hours a day had a substantial positive impact on pain and quality of life ratings. A randomized trial is required to validate these findings.

Alpha Lipoic Acid

Increased oxidative stress is one of the processes connected to the pathophysiology of diabetic neuropathy. Antioxidants have thus been investigated for their ability to limit oxidative stress, enhance the underlying pathophysiology of neuropathy, and lessen pain. A number of prospective, placebo-controlled trials have linked the powerful antioxidant alpha-lipoic acid (ALA) with a benefit for symptomatic diabetic neuropathy. In the SYDNEY 1 study, three weeks of daily intravenous ALA treatment were linked to lessened numbness, paresthesia, and discomfort. In the SYDNEY 2 trial, 181 patients with diabetes and symptomatic distal symmetric polyneuropathy were randomized to receive either a placebo for five weeks or one of three oral ALA doses (600, 1200, or 1800 mg daily). The following discoveries were made and reported:

In comparison to placebo, all three dosages of oral ALA therapy were linked to a statistically significant decrease in the neuropathy total symptom score, which includes stabbing, burning, paresthesia, and sleeping numbness. The benefits of ALA were dose-invariant.

50 to 62 percent of patients treated with ALA compared to 26 percent with placebo showed a clinically meaningful response, which was defined as a 50 percent reduction in neuropathic symptoms. The best dose of ALA was found to be 600 mg once daily since greater amounts were too likely to cause unpleasant side effects such nausea, vomiting, and dizziness without improving effectiveness. Given the trial's brief lifespan, these results' robustness is constrained. Alpha-lipoic acid's impact on how quickly neuropathy develops has not been examined in long-term trials.

Research Article (ISSN: 2834-5673)

For patients with symptomatic painful diabetic polyneuropathy who are refractory to or intolerable of antidepressants (such as amitriptyline, duloxetine, venlafaxine) or anticonvulsants (such as pregabalin) that have been shown to be effective for this condition, we instead recommend treatment with oral ALA 600 mg once daily.

Opioids

Opioids have been researched as potential treatments for painful diabetic neuropathy.

Dextromethorphan, an N-methyl-D-aspartate (NMDA) receptor antagonist and weak sigma opioid receptor agonist, was marginally more effective than a placebo in two small studies for treating diabetic neuropathy patients' pain.

Tramadol, at an average dose of 210 mg per day, was more effective than a placebo at reducing pain in two small randomized, double-blind studies. Nausea, constipation, headaches, and sleepiness were the most frequent side effects.

Two randomized clinical trials have demonstrated that controlled release (CR) oxycodone at a daily dose of 10 to 60 mg is both effective and safe for treating painful diabetic polyneuropathy. In the bigger of these trials, which included 159 patients, oxycodone CR at an average dose of 37 mg daily (range 10 to 99 mg daily) reduced pain more effectively than placebo.

The trials supporting the efficacy of opioids such as tramadol and oxycodone CR are all limited by short-term follow-up. A 2009 systematic review of opioids for chronic noncancer pain found a paucity of evidence regarding the long-term effectiveness and risks of such treatment, including the potential for opioid abuse, addiction, and overdose. Similarly, a 2013 systematic review noted that the available randomized controlled trials of opioids for neuropathic pain did not clearly address the issues of abuse and addiction.

In a cohort study of over 9900 patients prescribed long-term opioid therapy for

The trials supporting the efficacy of opioids such as tramadol and oxycodone CR are all limited by short-term follow-up. A 2009 systematic review of opioids for chronic noncancer pain found a paucity of evidence regarding the long-term effectiveness and risks of such treatment, including the potential for opioid abuse, addiction, and overdose. The same systematic review from 2013 found that the existing randomized controlled trials of opioids for neuropathic pain did not adequately address the problems of abuse and addiction.

In a cohort trial involving more than 9900 patients who received long-term opioid therapy for nonmalignant pain, higher-dose regimens were linked to a higher risk of opioid overdose. Because of these problems, some medical professionals no longer recommend using opioids to treat severe diabetic neuropathy. Given the paucity of evidence for long-term effectiveness and the risk of tolerance, addiction, and overdose, we advise against taking opioids to treat severe diabetic neuropathy.

Combination Therapy

Findings from short trials indicate that combinations of medications from various pharmaceutical classes are marginally more effective than monotherapy for treating neuropathic pain.

In a single-center randomized trial including 44 patients with neuropathic pain (the majority of whom had diabetic polyneuropathy), gabapentin plus morphine reduced mean pain intensity during the fourth week of treatment more effectively than either drug alone (mean, gabapentin 1705 mg and morphine 34 mg in combination). The combined

Research Article (ISSN: 2834-5673)

therapy's most common side effects were dry mouth, sedation, and constipation. A similar single center randomized trial of 47 patients (most with diabetic polyneuropathy) found that the combination of nortriptyline with gabapentin was more effective than either agent alone for reducing the mean intensity of daily pain during week four of treatment at the maximum tolerated daily dose (mean, nortriptyline 50 mg and gabapentin 2180 mg in combination). In both reports, the benefit of the combination treatment was small but statistically significant.

Electrical Nerve Stimulation

Although data are limited, a 2010 statement from the American Academy of Neurology (AAN) assessing the use of TENS for pain in neurologic disorders concluded that TENS is probably effective for reducing pain from diabetic polyneuropathy, based on following evidence:

One trial assigned 31 patients with chronic painful diabetic neuropathy to either TENS or sham treatment to the legs for 30 minutes daily for four weeks. Symptomatic improvement (of at least one grade on a unique zero to five scale) occurred in 15 of 18 patients (83 percent) with TENS treatment, compared with five of 13 patient's percent) who received sham treatment (odds ratio 6, 95% CI 1.1-33.4). Another experiment included 19 individuals with mild to moderately symptomatic diabetic polyneuropathy. At six and twelve weeks, active TENS treatment reduced the overall symptom score statistically significantly compared to sham treatment. Moreover, TENS therapy was linked to a statistically significant but minor improvement in pain on the visual analogue scale at six weeks. A subsequent 2011 guideline from the AAN evaluating the treatment of painful diabetic neuropathy concluded that percutaneous electrical nerve stimulation is probably effective, based upon three small trials. However, the percutaneous techniques evaluated in the 2011 AAN guideline are not widely available in clinical practice.

Other Interventions

Several other approaches have been tried in patients with painful diabetic neuropathy.

Acetyl-L-Carnitine

The amino acid L-acetylated carnitine's ester, acetyl-L-carnitine (ALC), has been studied in individuals with diabetic peripheral neuropathy. ALC 1000 mg (but not 500 mg) three times daily was related with significant improvement in pain levels in one of the studies and in the combined cohort, according to findings from two identically designed randomized controlled trials involving 1257 patients with diabetic polyneuropathy. Particularly given that significant improvement was not observed in either trial or at the lower dose of ALC, the benefit of ALC has to be confirmed.

Isosorbide

In 22 diabetic patients, an isosorbide dinitrate topical spray placebo-controlled pilot research showed a substantial reduction in total neuropathic pain and burning sensation.

Nsaids

In individuals with musculoskeletal or joint abnormalities brought on by chronic neuropathy, nonsteroidal anti-inflammatory medications (NSAIDs) are beneficial; in fact, joint deformities may be the main source of pain. In people with diabetic neuropathy, ibuprofen (600 mg four times day) and sulindac (200 mg twice daily) can both significantly reduce pain.

Research Article (ISSN: 2834-5673)

Theoretically, because NSAIDs impede prostacyclin synthesis, they could aggravate nerve damage and reduce nerve circulation. Until this potential has been thoroughly investigated, cautious use of this class of medications is advised.

Spinal Cord Stimulation

Implantable electrodes that transmit electrical stimulation to the spinal cord's dorsal columns are used in spinal cord stimulation, an invasive procedure. In individuals with painful, refractory diabetic neuropathy affecting the legs, preliminary data from a small open-label trial indicate that spinal cord stimulation lessens pain. To verify this method's effectiveness, additional studies are required.

Guidelines

In 2011, the American Academy of Neurology (AAN) conducted a systematic study and released treatment recommendations for painful diabetic neuropathy. The subsequent findings were made: Pregabalin (300 to 600 mg per day) was considered to be efficient.

Some therapies were thought to be probably effective:

Gabapentin (900–3600 mg/day), Sodium valproate (500–1200 mg/day), Amitriptyline (25–100 mg/day), Duloxetine (60–120 mg/day), Venlafaxine (75–225 mg/day), Dextromethorphan (400 mg/day), and Morphine Sulfate (titrated to 120 mg/day) are all examples of medications. Oxycodone (mean 37 mg/day, maximum 120 mg/day), Tramadol (210 mg/day), Capsaicin (0.075 percent four times/day), Isosorbide Dinitrate Spray, Percutaneous Electrical Nerve Stimulation for 3–4 Weeks, and Lidocaine Patch were all considered to be potentially helpful.

The AAN regarded oxcarbazepine, lamotrigine, lacosamide, clonidine, pentoxifylline, mexiletine, magnetic field therapy, low-intensity laser therapy, and Reiki therapy as likely ineffective treatments. The American Diabetes Association (ADA) produced a statement in 2005 outlining a management algorithm that advised therapy in the following sequential order: Exclude nondiabetic etiologies

- Stabilize glycemic control (insulin not always required in type 2 diabetes)
- Tricyclic drugs (e.g., amitriptyline 25 to 150 mg before bed)
- Anticonvulsants (e.g., gabapentin, typical dose 1.8 g/day)
- Opioid or opioid-like drugs (e.g., tramadol or controlled release oxycodone)
- Consider pain clinic referral

The ADA statement noted that nonpharmacologic, topical, or physical therapies might be useful at any stage. These measures include acupuncture, capsaicin, glyceryl trinitrate spray or patches, and other therapies.

Choice Of Therapy

We advise starting individuals with painful diabetic neuropathy on one of the above-mentioned antidepressants (such as amitriptyline, duloxetine, or venlafaxine) or anticonvulsants (such as pregabalin). Even though there aren't many high-quality comparative trials, the evidence so far points to a comparable modest benefit for these drugs. Because it is effective and affordable, amitriptyline is the medication we like to start with, especially in younger, healthier patients. One of these medications may be shifted to monotherapy with another agent for patients who do not improve after a reasonable trial. The next stage in the treatment paradigm for patients who do not respond to one medicine is combination therapy, which uses two pharmaceuticals from different therapeutic groups. Other therapies

Research Article (ISSN: 2834-5673)

for patients who are unable to take any of these medications include capsaicin cream, a lidocaine patch, alpha-lipoic acid, a topical spray of isosorbide dinitrate, and transcutaneous electrical nerve stimulation. Opioids are controversially used to treat persistent non-cancerous pain. We advise against using opioids to treat painful diabetic neuropathy due to the absence of long-term effectiveness evidence and the risk of opioid tolerance, addiction, and overdose. Nonetheless, despite these reservations, some experts think that opioids can help treat painful diabetic neuropathy. Glycemic management may or may not play a part in established diabetic neuropathy. However in individuals with type 2 diabetes, rigorous glycemic control is linked to a decreased risk of microvascular problems, and intensive therapy may lower the risk of macrovascular consequences in such patients. Moreover, patients with type 1 diabetes who maintain strict glucose control experience fewer microvascular and macrovascular problems. Each of these concerns is covered in depth independently.

Non-Glycemic Measures

Potential treatments for diabetic neuropathy include aldose reductase inhibitors and multifactorial risk factor reduction.

Multi Factorial Risk Factor Reduction

The potential efficacy of intensive combined therapy in patients with type 2 diabetes and microalbuminuria was examined in the Steno type 2 trial. In this prospective study, 160 patients were randomly assigned to standard or multifactorial intensive therapy. The intensive regimen consisted of behavioral therapy (including advice concerning diet, exercise, and smoking cessation) and pharmacologic intervention (consisting of the administration of multiple agents to attain several aggressive therapeutic goals). Diabetic autonomic and peripheral neuropathy were present at baseline in 28 and 34 percent, respectively. During a mean follow-up of 7.8 years, there was no slowing of peripheral neuropathy progression in the intensive therapy group but a considerably reduced rate of development of autonomic neuropathy (30 versus 54 percent, relative risk 0.37).

Aldose Reductase Inhibitors

A proposed alternative strategy to lowering blood glucose levels is reducing the toxicity of hyperglycemia. If sorbitol accumulation contributes to diabetic neuropathy, then using an aldose reductase inhibitor to stop sorbitol synthesis would be advantageous.

Aldose reductase inhibitors have shown variable results in diabetic neuropathy in the research that are currently available. Each piece of evidence is given in great detail.

Surgical Decompression

The Dellon treatment is a controversial approach for treating diabetic polyneuropathy that involves surgically decompressing several peripheral nerves. According to the theory supporting surgical decompression, the metabolic stress of diabetes makes peripheral nerves vulnerable to compressive injury at locations of possible nerve entrapment, and that several peripheral nerves being injured at once is what causes symptoms in the majority of patients. However, there are no adequately designed trials to support the use of surgical decompression of multiple peripheral nerves as a treatment for symptomatic diabetic polyneuropathy. Therefore, this treatment is not recommended.

Research Article (ISSN: 2834-5673)

Duloxetine HCL

The treatment of pain brought on by diabetic peripheral neuropathy has recently received FDA approval.

An antidepressant medication is called duloxetine HCl. This substance blocks the reuptake of serotonin and norepinephrine. Osteoarthritis and musculoskeletal discomfort can both be treated with duloxetine. Moreover, it can treat fibromyalgia symptoms and ease severe peripheral neuropathy symptoms, especially diabetic neuropathy. A 2014 comprehensive review found that the dual serotonin and norepinephrine reuptake inhibitor duloxetine is beneficial in treating diabetic polyneuropathy pain. In three 12-week randomized, blinded, controlled trials including 1102 participants, the benefit of duloxetine was proven. Duloxetine 60 or 120 mg daily considerably outperformed a placebo in these trials at relieving pain (47 and 48 percent, versus 29 percent with placebo) The first week of treatment saw a noticeable decrease in pain, and this improvement persisted throughout the whole study. Duloxetine was beneficial in reducing pain at night and had a quick onset of action and sustained improvement. Although both doses were effective, the 120 mg daily dose was not tolerated as well as the 60 mg daily dose. While being more successful than a placebo in all three trials, the long-term efficacy and safety of duloxetine are unknown. Duloxetine medication also led to slight elevations in fasting plasma glucose in clinical trials looking at painful diabetic polyneuropathy. Amitriptyline looks to be as effective as duloxetine for treating painful diabetic neuropathy and is more affordable, despite the fact that comparable trials are rare. Duloxetine's most often reported side effects were constipation, nausea, sleepiness, and vertigo. Also infrequently mentioned were hot flashes and erectile problems. The medicine should be taken on an empty stomach because nausea is frequently experienced by patients. Anticonvulsant medication can be coupled with duloxetine, however it shouldn't be taken with other serotonin or norepinephrine uptake inhibitors.

Metformin

The first-line treatment for type 2 diabetes is metformin, which is sold among other trade names as Glucophage. This is especially true for overweight people. Moreover, polycystic ovarian syndrome is treated with it. Metformin may be able to prevent diabetes consequences like cancer and cardiovascular disease, according to scant research. It has no connection to weight gain. It is ingested orally. Most people tolerate metformin well. Diarrhea, nauseousness, and abdominal pain are typical side effects. Low blood sugar is unlikely to occur with it. If prescribed incorrectly and in excess, high blood levels of lactic acid are a risk. Those who have kidney or liver illness shouldn't use it. Insulin is typically favored for gestational diabetes even though there is no obvious damage if given during pregnancy. The biguanide class includes metformin. It functions by reducing liver glucose synthesis and enhancing body tissue glucose uptake. In 1922, the drug metformin was found. French physician Jean Sterne started a human study in the 1950s. The United States and France both adopted it in 1995. It is among the most crucial drugs required in a fundamental healthcare system, according to the World Health Organization's List of Essential Medicines. The most popular oral diabetes medicine, according to research, is metformin. It is a generic drug that is readily available. As of 2014, the monthly wholesale price ranges from 0.21 to 5.55 USD. It costs between USD 5 and USD 25 a month in the United States.

Research Article (ISSN: 2834-5673)

While being used more frequently for polycystic ovarian syndrome, metformin is primarily utilized for type 2 diabetes.

Plan Of Work

Literature survey

Selection of suitable drug candidate

Selection of polymers

Preformulation studies of Duloxetine Hydrochloride and metformin.

a. Identification studies (physical state, melting point, solubility)

b. Construction of calibration curve.

c. Micrometric properties.

d. To study the drug and excipients compatibility by FTIR studies

e. Preparation and optimization of core tablet (Duloxetine Hydrochloride).

f. Preparation and evaluation of Press-coated tablets (Duloxetine Hydrochloride)

g. Preparation and evaluation of immediate release tablet (Metformin).

h. Tablets enclosed in capsules (Duloxetine HCl press-coated tablets and Metformin HCl).

LITERATURE REVIEW

Reddy et al. (2004) used direct compression to create an oral press-coated tablet. This press-coated tablet was created with a barrier layer made of several magnesium stearate compositions and an inner core containing duloxetine. The impact of formulation parameters on a barrier layer made up of both hydrophobic and hydrophilic excipients

According to Janugade B. et al. (2005), an oral press-coated tablet was made employing the direct compression and wet granulation procedures to obtain the desired lag time. The exterior barrier layer of this press-coated tablet, which contains montelukast sodium in the inner core, was created using various combinations of the hydrophobic polymer ethyl cellulose and the hydrophilic low-substituted hydroxypropyl cellulose. The impact of formulation composition on the barrier layer, which includes both hydrophobic and hydrophilic excipients, on the delay in drug release was examined. It was found that as the concentration of low-substituted hydroxypropyl cellulose increases, the lag time reduces. Press-coated pills coated using dry mixing and wet granulation displayed different lag times. The wet granulation method has less lag time than the dry mixed blend method.

The major goal of this work, according to Raja Subburayalul et al. (2006), is to create stable Duloxetine HCl delayed release pellets with the help of a nonionic protective layer between the drug layer and enteric layer. The acidic atmosphere makes duloxetine HCl very unstable. Because the enteric polymer contains free acid, the Preformulation investigation showed that duloxetine HCl is incompatible with them. A pH of alkaline also makes duloxetine HCl unstable. This is why barrier coating uses a nonionic polymer. The fluidized bed process was used to create varying amounts of barrier coating for the duloxetine hydrochloride enteric coated pellets.

Research Article (ISSN: 2834-5673)

Three separate layers, the drug layer, the barrier layer and the enteric layer, were coated onto the inert core pellets, sugar spheres. The enteric coated pellets were top coated using film coating material and encapsulated in hard gelatin capsule shell. The probability of interaction of the enteric polymer with

duloxetine is very high during shelf life. The filled capsules were evaluated for description, Assay, Acid resistance and Drug release in pH 6.8 Phosphate buffer at initial and 6 months accelerated condition (40 ± 2°C/75± 5%RH), to conclude the % buildup of barrier coating required to avoid the interaction between duloxetine hydrochloride and an enteric polymer. Duloxetine hydrochloride interacts with an enteric polymer, although the formulation with 10% and 15% barrier coating fails to prevent this. Duloxetine hydrochloride's interaction with the enteric polymer was kept under control in the formulation with 20% barrier coating.

Including St. Louis (2004) In 2004, the first drug, duloxetine, a balanced selective serotonin-norepinephrine reuptake inhibitor (SNRI), was given regulatory approval in the US to treat severe diabetic neuropathy. This substance reduces or controls the symptoms of diabetic neuropathy and has no other notable receptor or channel actions besides the mechanisms for inhibiting serotonin and norepinephrine reuptake. Duloxetine has no known neuroprotective or other effects which prevent the development of neuropathy in patients with diabetes. The purpose of this review article is to discuss the background of painful diabetic neuropathy, the pharmacology of duloxetine, and its safety and efficacy in clinical trials and long- term observations. The authors will also comment on its use in clinical practice. Results from controlled clinical trials reveal that duloxetine administered at 60 mg qd or 60 mg bid is efficacious in treating diabetic neuropathic pain relative to placebo. Positive treatment outcomes are also seen for other measures of pain and quality of life. In controlled clinical trials, there was a little but statistically significant rise in blood glucose levels compared to placebo-treated subjects. Otherwise, controlled and open-label clinical investigations have shown that the drug is highly safe and tolerable. These data support the hypothesis that serotonin and the brainstem and spinal cord's descending pain inhibition circuits are primarily mediated by norepinephrine.

Queen Square et al, (2010) duloxetine is a balanced serotonin and noradrenaline reuptake inhibitor licensed for the treatment of major depressive disorders, urinary stress incontinence and the management of neuropathic pain associated with diabetic peripheral neuropathy. A number of trials have been conducted to investigate the use of duloxetine in neuropathic and nociceptive painful conditions. This is the first update of a review first published in 2010.

According to Michelle.J et al (2012), diabetic peripheral neuropathic pain (DPNP) is the most prevalent and incapacitating of the diabetic neuropathies and can impact up to 70% of diabetics. In patients who are impacted, DPNP dramatically lowers quality of life and raises management expenditures. Despite the effects of DPNP, management is subpar, with 25% of patients receiving no treatment and many receiving medicines that is ineffective or hardly works. Duloxetine is one of two drugs approved by the United States Food and Drug Administration for DPNP management. Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) proven safe, effective, and cost-saving in affected patients. Despite the impact factor of DPNP, management is poor with one-quarter of patients receiving no treatment and many treated with medications having little or no efficacy in managing DPNP. Duloxetine is one of two drugs approved by the United States Food and Drug Administration for DPNP

Research Article (ISSN: 2834-5673)

management. Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) proven safe, effective, and cost-saving in reducing DPNP symptoms at a dose of 60 mg/day. Duloxetine doses greater than 60 mg/day for DPNP management are not recommended since they are no efficacious and associated with more side effects; the addition of pregabalin or gabapentin for these patients may be beneficial. Duloxetine's side effects are often modest and include those that are typical of the SNRI class, such as nausea, drowsiness, fatigue, sweating, dry mouth, constipation, and diarrhea. Duloxetine is an excellent option for DPNP treatment in individuals with comorbid depression, anxiety, fibromyalgia, or persistent musculoskeletal pain, given its other indications. Diabetes patients' glycemic control was unaffected by duloxetine medication, and the risk of cardiovascular events was not raised. However, people with severe renal impairment or hepatic illness should not use duloxetine. Duloxetine is a fantastic option for many people seeking DPNP treatment due to its safety, effectiveness, and tolerability.

According to Kammela K. Chakravarthy et al. (2014), the goal of the current study is to create and assess Omeprazole delayed release pellets that are equivalent to the innovator product. The enteric film coating procedure was used to create different drug loading, barrier coating, and enteric coating compositions for Omeprazole delayed release pellets. Enteric polymers included Eudragit L 100 55 and HPMC Phthalate 55 S. The various batches were tested for assay/drug content, water content, acid resistance, and dissolving rate after the process variables were standardized. The produced formulations of omeprazole delayed release were compared to the innovators' product's drug dissolving profiles. The formulation containing enteric coating polymer HPMC-P 55 S (12%) and plasticizers diethyl phthalate that produced the greatest results for Omeprazole delayed release pellets was acetyl alcohol.

Using an enteric coating made of methacrylic acid copolymer and a subcoating made of hydroxypropyl methyl cellulose, the current investigation's goal was to manufacture delayed release pellets of rabeprazole sodium. By stacking a medication suspension, the various pellet batches were created. The final batch exhibited a good degree of resemblance to market items after a comparison of the dissolution profile of the final batch with market preparations. The final formulation had excellent storage conditions, according to the findings of the accelerated stability test.

S.K.Singh*1 at al,(2018) pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5mm to 1.5mm, and are intended usually for oral administration. Pellets can be prepared by many methods, the compaction and drug-layering being the most widely used today1. The study was undertaken with an aim to develop delayed release micro pellet dosage form for Lansoprazole which is a benzimidazole anti-ulcer agent and is one of the most widely used drugs for treating mild and severe ulcers. The current study's methodology involved comparing these polymers and excipients and evaluating the impact of the active components' physicochemical properties on the drug release profile. Fluid bed coater (FBC) with air pressure 2.0 bar and spray rate 10-15ml/min was used to create the prototype formulation for micro pellets. The temperature of the bed is varied between 35 and 50 degrees Celsius, while the temperature at the inlet is varied between 50 and 70 degrees Celsius. The effects of various parameters, including air pressure, the temperature at the inlet and outlet of the FBC, were observed. It is noted that at high pressure, the pellets break. The formulation exhibits lumps at low temperatures, and at 2.0 bar air pressure, an inlet

Research Article (ISSN: 2834-5673)

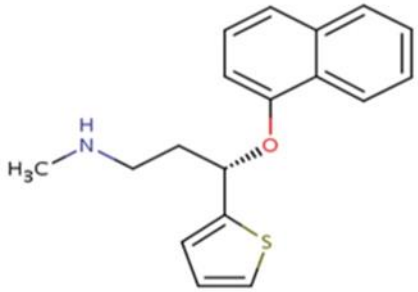
temperature of 60°C and a bed temperature of 40°C are reliable for a solution flow rate of 10-15 ml/min. About the outcomes of the prototype Lansoprazole preparation, the Micro pellets were made using HPMC E5 polymer as a release retardant in three distinct concentrations, i.e., 40%, 50%, and 60% For enteric coating, 8%, 10%, and 12% of NaOH and Acrycoat L30D solution were utilized. Formulated micro pellets exhibited delayed in vitro dissolving behavior, most likely as a result of the polymer's optimal concentration. After three months, the micro pellets medication remained stable at room temperature, 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH in accordance with ICH recommendations.

Drug And Excipient Profile

Duloxetine Hydrochloride

Drug name : Duloxetine Hydrochloride

Structure : fig .no: 2 structure of DLX HCL



IUPAC name : methyl (3s)-3-(naphthalene-1-yloxy)-3-(thiophen-2-yl)propyl amine

Mol formula : C18H19NOS

Mol. Wt. : 297.41456 g/mol

Appearance : White powder

Solubility : Duloxetine is poorly soluble in water

Dose : 60-120mg/day

Half life : 12hrs

Category : Anti – Depressant, Diabetic Peripheral neuropathy

Melting point : 160 -170°C

Drug p^{Ka} : 9.7

Clinical Pharmacology

Mechanism Of Action

Serotonin and norepinephrine reuptake in neurons are strongly inhibited by duloxetine, while dopamine reuptake is very weakly inhibited. Opioid, glutamate, GABA, dopaminergic, cholinergic, histaminergic, cholinergic, and cholinergic receptors are not significantly influenced by duloxetine. It is thought that duloxetine's ability to potentiate serotonergic and noradrenergic activity in the Brain underlies both its antidepressant and pain-inhibiting

properties. Duloxetine's mechanism of action in SUI has not been identified, although it is likely related to the potentiation of serotonin and norepinephrine activity in the spinal cord, which raises urethral closure forces and lessens involuntary urine loss.

Pharmacokinetic

Absorption: administered duloxetine hydrochloride is well Orally absorbed.

Distribution **:** 1640L

Protein binding : Protein binding is greater than 90

Metabolism

The main biotransformation mechanisms for duloxetine involve oxidation of the naphthyl ring, conjugation, and further oxidation. In vitro, the naphthyl ring oxidation is catalysed by CYP2D6 and CYP1A2. Plasma contains the metabolites 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulphate. It has not been demonstrated that the primary circulating metabolites significantly contribute to the pharmacologic activity of duloxetine.

Route Of Elimination

Urine contains a large number of other metabolites, some of which are merely minor elimination pathways. The majority of the duloxetine dose (about 70%) is eliminated in the stool as over 205 different duloxetine metabolites.

Uses

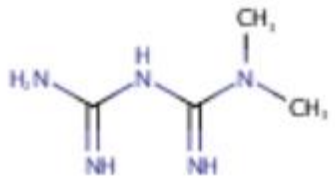
Management of chronic musculoskeletal pain.

- Management of Diabetic Peripheral neuropathy.
- Management of fibromyalgia.
- Treatment of generalized anxiety disorder (GAD).
- Treatment of major depressive disorder (MDD).

Metformin

Drug name :Metformin hydrochloride

Structure: fig no:3 structure of metformin



- IUPAC name :1-carbamimidamido-N,N-dimethyl amide
- Mol formula :$C_4H_{11}N_5$
- Mol weight :129.1636 g/mol
- Appearance :white powder
- Route of administration :Oral

Research Article (ISSN: 2834-5673)

- Solubility :Freely soluble in water as HCL salt (1.38 mg/ml)
- Dose :

Immediate Release

Initial dose: 500 mg orally twice a day or 850 mg orally once day

Dose titration: Increase in 500 mg weekly increments or 850 mg every 2 weeks as tolerated.

Maintenance dose:2000mg daily

Maximum dose :2550mg daily

Extended Release

Initial dose: 500-1000 mg orally once a day

Dose titration: Increase in 500 mg weekly increments as tolerated

Maintenance dose: 2000 mg daily

Maximum dose: 2500 mg daily

- Protein binding :Minimal
- Metabolism : Not by liver
- Excretion : Urine (90%)
- Bioavailability : 50-60%
- Half life : 6.2 hours
- Category : Anti-diabetic
- Melting point : 223^{o}C -226^{o}C
- Drug p^{Ka} : 12.4

Mechanism Of Action

Metformin reduces hyperglycemia primarily by inhibiting liver glucose synthesis (hepatic gluconeogenesis). The "average" person with type 2 diabetes produces three times as much gluconeogenesis as is healthy; metformin therapy lowers this rate by more than one-third. The molecular mechanism of metformin is incompletely understood: inhibition of the mitochondrial respiratory chain (complex -1), activation of AMP activated protein kinase (AMPK), inhibition of glucagon-induced elevation of cyclic adenosine monophosphate (cAMP), and consequent activation of protein kinase A (PKA), inhibition of mitochondrial glycerophosphate dehydrogenase, and an effect on gut microbiota have been proposed as potential mechanisms. Metformin suppresses hepatic glucose synthesis in addition to improving insulin sensitivity, enhancing peripheral glucose uptake (by causing the phosphorylation of GLUT4 enhancer factor), and reducing gastrointestinal glucose absorption. Improved insulin binding to insulin receptors may explain the increased peripheral utilization of glucose. Patients with NIDDM have also shown increased insulin binding following metformin treatment.

MEDICINAL USES: Metformin is primarily used for type 2 diabetes but is increasingly being used in polycystic ovary syndrome.

Magnesium Stereate

Research Article (ISSN: 2834-5673)

Non-proprietary name

BP: Magnesium Stearate

JP: Magnesium Stearate

PhEur: Magnesium Stearate

USP-NF: Magnesium Stearate

Synonyms

Dibasic magnesium stearate : Octadecanoic acid

Magnesium Di stearate : Magnesium salt

Magnesii stearas : Stearic acid, magnesium salt

Magnesium octadeanoate : Synpro90

Chemical name : Octadecanoic acid magnesium salt [557-04-0]

Empirical Formula : $C_{36}H_{70}MgO_4$

Molecular Weight : 591.24

Functional Category : Tablet and capsule lubricant

Melting Point : 117-150ºC

Description:

Magnesium stearate is a very fine, light, white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Stability and Storage Conditions:

Magnesium stearate is stable and should be stored in a well closed container in cool, dry place.

Sodium Starch Glycolate:

Nonproprietary Names:

BP: Sodium Starch Glycolate

PhEur: Sodium Starch Glycolate

USP-NF: Sodium Starch Glycolate

Synonyms:

Carboxymethyl starch Primojel

Sodium salt Starch carboxymethyl ether

Carboxyl methylamylumnatricum Sodium salt

Explosion Tablo

Explotab VivastarP

Glycolysis

Chemical Name : Sodium Carboxymethyl Starch

Chemical Formula :$C_{24}H_{44}O_6Na$

Research Article (ISSN: 2834-5673)

Molecular Weight : 222.25

Functional Category **:** Tablet and Capsule disintegrant.

Stability and Storage Conditions:

Tablets prepared with sodium starch glycolate have good storage properties. (22-24) Sodium starch glycolate is stable although very hygroscopic, and should be stored in a well-closed container in order to protect it from wide variations in humidity and temperature, which may cause caking. The physical properties of sodium starch glycolate remain unchanged for up to 3 years if it is stored at moderate temperatures and humidity.

Incompatibilities:

Sodium starch glycolate is incompatible with ascorbic acid.

TALC:

Nonproprietary Names:

BP: Purified Talc	PhEur: Talc
JP: Talc	USP: Talc

Synonyms:

Altaic	Magsil Star; powdered talc
E553b	Purified French chalk
Hydrous magnesium calcium silicate	Purtalc
Hydrous magnesium silicate	Soapstone
Imperial	Steatite
Luzena Pharma	superior
Magnesium hydrogen metasilicate	Talcum
MagsilOsmanthus	

Chemical Formula : $Mg_3Si_4O_{10}(OH)_2$

Molecular Weight : 379.27 gm

Melting Point :1500ºC

Functional Category:

Anticaking agent, glidant tablet and capsule diluents, tablet and capsule lubricant.

Description:

Talc is a very fine, white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Stability and Storage Conditions:

Talc is a stable material and may be sterilized by heating at 1608ºC for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation10). Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities: Incompatible with quaternary ammonium compounds.

CALCIUM PHOSPHATE:

Research Article (ISSN: 2834-5673)

Non-proprietary Names:

BP: Anhydrous Calcium Hydrogen Phosphate

JP: Anhydrous Dibasic Calcium Phosphate

PhEur: Calcium hydrogen Phosphate, Anhydrous

USP: Anhydrous Dibasic Calcium Phosphate

Synonyms:

Calciihydrogenophosphasanhydrous dicalcium orthophosphate

Calcium mono-hydrogen phosphatesecondary calcium phosphate

Calcium orthophosphate

Chemical Name **:** Dibasic calcium phosphate

Molecular Formula : $CaHPO_4$

Molecular Weight :136.06

Functional Category : Tablet and Capsule diluent

Description:

Anhydrous dibasic calcium phosphate is a white, odourless, tasteless, powder or crystalline solid. It occurs as triclinic crystals.

HPMCP:

Nonproprietary Names:

BP: Hypromellose Phthalate

JP: Hypromellose Phthalate

PhEur: Hypromellose Phthalate

USP-NF: Hypromellose Phthalate

Synonyms:

Cellulose phthalate hydroxypropyl methyl ether

HPMCP

Hydroxypropyl methylcellulose benzene-1,2-dicarboxylate

2hydroxypropyl methylcellulose phthalate

Hypermellosephthalates

Mantrocel HP-55

Methyl hydroxypropyl cellulose phthalate

Application: Gastro-resistant polymers are insoluble at aid $p^H<5$ and become soluble as the p^H increases. Therefore, they maintain the integrity of APIs in the stomach and release them in the intestine.

Chemical Name : Cellulose, hydrogen 1,2-benzenedicarboxylate,2-hydroxypropyl

Description : White to off- white colour with free-flowing flakes or granules, odourless. Flakes or as agranular powder. It is odourless or with a slightly acidic odour and has a barely detectable taste.

Hypromellose phthalate occurs as white to slightly off-white, free – flowing.

Research Article (ISSN: 2834-5673)

Melting Point : 150°C

Molecular Weight : 508.42 gm/m

Solubility:

Readily soluble in alcohol of acetone methyl of ethyl alcohol(1:1)

They also protect the gastric mucosa from irritating API's. Using film-coating, the bioavailability of some drugs can be increased by controlling the release of the APIs in the intestine. The bioavailability of some API's is better in the intestine than in the stomach.

Viscosity: 32-48cSt

RESOURCES AND TECHIQUES

A. Drug and excipients procurement

The following supplies and equipment are of laboratory quality and were utilized in the experiment.

Table2: Details of the materials used.

Sl. no	Materials	Purpose
1	Duloxetine HCl	Anti-depressant Diabetic-Peripheral Neuropathy
2	Metformin	Anti-diabetic
3	Sodium starch glycolate	Super disintegrant
4	Calcium phosphate	Diluents
5	Magnesium state	Lubricant
6	Talc	Glidant
7	HPMCP	Polymer

B. Instruments and equipment's used:

Table 3: Details of equipment used:

Sl. No	Equipment	Model/Company
1	Electronic balance	Ocean-DJ302A
2	Fourier transformer infrared	Bruker
3	U.V-Visible spectrophotometer	Thermo scientific
4	Tablet compression machine	General pharmaceutical punch machine
5	Hardness tester	Dolphin, India
6	Friability test apparatus	Roche friability, India
7	pH meter	Eli co LI 120
8	Dissolution test apparatus	Lab India DS8000
9	Disintegration test apparatus	Dolphin, India

Research Article (ISSN: 2834-5673)

METHODOLOGY

Studies On Preformulation

The physical and chemical characteristics of pharmacological compounds alone and when coupled with excipients are examined in Preformulation investigations. It is the initial stage in the creation of the dosage form formulation. The main flaw in Preformulation testing is that it produces data that can be used to create a stable and bioavailable dosage form. Preformulation studies are used to reduce the influence of formulation changes on acceptable consumption, effectiveness, and a stable product.

Identification

Calibration Technique

The duloxetine hydrochloride standard solution was made by precisely weighing 10 mg of the medication and diluting it in 100 ml of volumetric flask with distilled water to provide a range of solutions with a final concentration of 5–50 ug/ml. The solubility of every solution at 290 nm was found.10mL volumetric flasks were used to collect samples equating to 5–25 g, which were then filled with methanol. These solutions' absorbance was measured at 292 nm using methanol as a reference. An adjustment curve was plotted.

Phosphate buffer 6.8:

In a volumetric flask, dissolve 28.80 grammes of disodium hydrogen phosphate and 35.084 grammes of di-sodium hydrogen phosphate. Then, add enough water to make 1000 milliliters.

Acid buffer1.2:

Measure 8.5 ml of HCI into the 1000 ml volumetric flask for the acid buffer step. Makeup with up to 1000ml of water.

Building a stock solution:

10mg of pure duloxetine hydrochloride, which was precisely weighed, was dissolved in 10ml of 6.8 phosphate buffer.100ml of 6.8 phosphate buffer were added to 1 ml of the solution.

Making the standard solution:

After adding 6.8 phosphate buffer, the aforementioned solution was diluted to produce a series of solutions that each included 10, 20, 30, 40, and 50 g of duloxetine hydrochloride per ml of solution. Using a UV Spectrophotometer and 6.8 phosphate buffer as the measuring medium, the absorbance of the aforementioned dilutions was determined at 290 nm.

Melting Point:

Using a capillary tube, melting point was illustrated. The medication is administered through a capillary tube that was put into a melting point instrument and pointed at Both the point at which the medication chirrups begin and the point at which it finishes completely were observed.

Solubility:

Water, methanol, DMSO, ethanol, and other substances were tested to see how soluble duloxetine was.

Comparability:

Research Article (ISSN: 2834-5673)

Knowledge of drug and excipients interactions is therefore very useful to the formulator in selecting appropriate excipients this information may already be in existence for known drugs. For new drugs are new excipients, the Preformulation scientist must generate the needed information.

The drug was mixed with excipients in1:1 ratio. These mixtures were kept in 5 ml glass transparent vials and pack properly and store at ambient conditions. Observations of physical appearance were made at initial in after one month. The samples were withdrawn for FT-IR analysis at the end of the study.

The infrared absorption spectra of pure drug, a physical mixture of polymer and drug were performed for polymer drug interaction studies between 4000cm-1to 400cm-1 by KBr pellet method.

Micrometric Properties: Microparticles are characterized by their micrometric properties like bulk density, tapped density, the angle of repose, Carr's index, husners ratio.

Angle of repose:

The angle of repose of powder blend was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the formula

Tan θ = h/r

θ = tan − 1 h/r ., where, θ = angle of repose, h = height, r = radius

Table 4: Flow properties

low property	Angle of repose (degrees)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Poor-must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	>66

Compressibility index

The compressibility index is a measure of the propensity of the powder to be compressed. As such, they are measures of the relative importance of inter-particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter-particulate interactions and a greater difference between bulk and tapped densities will be observed. These differences are reflected in the Compressibility index.

The compressibility index is calculated using measured values for bulk density (Db) and tapped density (Dt) as follows.

Research Article (ISSN: 2834-5673)

Compressibility Index = [Dt-Db/Dtx 100]

Hausner's ratio:

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material.

Effect of Carr's index and Hausner's ratio on flow property

$$Carr's index = \frac{tappeddensity - bulkdensity}{tappeddensity} * 100$$

$$Hauser's ratio = \frac{tappeddensity}{bulkdensity}$$

Carr's index (%)	Flow character	Hauser's ratio
≤10	Excellent	1.00–1.11
11-15	Good	1.12–1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

Formulation of core tablets:

The formulation was designed by mixing up 60mg of the drug i.e., Duloxetine HCl, sodium starch glycolate with varying concentrations from 0-8% as a super disintegrant, 1% of magnesium stearate as a lubricant, 1% talc which acts as a glidant and varying concentrations of lactose as diluents to maintain the uniform weight of the tablet.

Preparation of core tablets:

The inner core tablets were prepared by using direct compression method. The powder mixtures of duloxetine, sodium starch glycolate, talc, lactose followed by addition of magnesium Stearate. The mixtures were then mixed properly and powder blend was compressed using a 6mm punch and die to obtain the core tablets (F1 – F5).

Formulation of press coated tablet (HPMCP):

HPMCP was used in various concentrations varying from (0-10%) as a polymer for press-coating the core formulation (F4). To it, magnesium stearate, talc, lactose were added. This formulation is developed by the direct compression method by using 8mm punch.

Preparation press coated tablet:

HPMCP is press-coated on f4, which acts as an enteric polymer layer. The other excipients like magnesium stearate, talc, lactose were mixed together and were subjected to direct compression. These formulations are represented as

Research Article (ISSN: 2834-5673)

F41-F45. The thickness of the press-coated tablets was found to be 3.5-3.7mm.

Formulation of the press-coated tablet (Metformin):

Metformin is an outer coat of the tablet F44. This is compressed by using direct compression method by mixing up 500mg of metformin, 0-10% of sodium starch glycolate as a super disintegrant, magnesium stearate which acts as a lubricant, talc as a glidant and lactose to increase the bulk i.e., as a diluent. The tablets were compressed using 12mm punch.

Preparation of the press-coated tablet:

Metformin, sodium starch glycolate, magnesium stearate, talc, lactose were all mixed well together and were weighed exactly and compressed into a tablet by using a direct compression method. The thickness of the tablets F441-F445 was found to be 4.795-5.255mm.

Evaluation of tablets

Thickness

Tablet thickness is important for tablet packaging. The tablet thickness is determined by the diameter of the die, the amount of fill permitted to enter the die and the force or pressure applied during compression. The thickness of the tablet may be measured manually or by automatic equipment. The thickness of the tablets was measured by Vernier calipers. It is expressed in mm.

Hardness

The Monsanto hardness tester was used to gauge the tablet's hardness. A zero reading was taken once the bottom plunger made contact with the tablet. The tablet was finally broken by rotating a threaded bolt, which pulled the plunger up against a spring. A pointer moves along a gauge in the barrel to show the force as the spring is squeezed.

Weight variation:

20 pills were chosen, both individually and collectively weighed. The average weight was determined from the total weight. The weight of each tablet was then compared to the average weight to determine whether it was within the allowed range or not. At 300 mg, no more than two of the individual weights were more than 5% off from the average.

Table 6: limits for tablet weight variation test

Average weight of tablet(mg)	% difference allowed
130 (or) less	10%
From 130-324	7.5%
>324	5%

Friability test

10 previously weighed tablets were placed in the friability apparatus, which was given 100 revolutions and the tablets were reweighed. The percentage friability was calculated by using the following formula,

Percentage friability = [initial weight-final weight /initial weight × 100.]

Method

Research Article (ISSN: 2834-5673)

If the tablet weight is >650 mg 10 tablets were taken and initial weight was noted. For tablets of weight less than 650 mg, the number of tablets equivalent to a weight of 6.5 g was taken. The tablets were rotated in Roche Friabilator for 100 revolutions at 25 rpm. The tablets were dedusted and reweighed. The % friability should be not more than 1 % w/w of the tablets is being tested.

The % friability is expressed as the loss of weight and is calculated by formula

% Friability = [(who – wf) / wo] x 100

Wo – initial weight of tablets,

Wf – final weight of tablets

Disintegration:

If the tablet has a soluble external coating immerse the basket in water at room temperature for 5min.Suspend the assembly in the beaker containing 0.1MHcl and operate without discs for 120 min, unless otherwise stated in the individual monograph. Remove the assembly from the liquid. No tablet shows signs of cracks that would allow the escape of the contents of disintegration, apart from the fragments of the coating. Replace the liquid in the beaker with mixed phosphate buffer pH.6.8 add a disc to each tube and operate the apparatus for further 60min. remove the assembly from the liquid. The tablets pass the test if all six have disintegration.

In-vitro Dissolution:

Apparatus: USP APPARATUS II

Medium: 0.1N HCl up to 1st two hours,

pH 1.2 Phosphate buffer (pH 6.8 for) remaining hours Sampling interval: 5, 10, 20, 30,

45 & 60 minutes.

:RPM 100

Temperature: 37ºC± 0.5ºC

Procedure

Press-coated tablets F441, F442, F443, F444, and F445 were individually put into one of the six flasks that contained 900ml of 0.1N HCl for dissolving. Before, raise the temperature by 0.5°C to 37°C. Take samples every 5, 10, 20, 30, 45, and 60 minutes, then replace them. the medium with phosphate buffer 6.8, collect samples for the final 30 minutes not less than 1 cm from the vessel wall and halfway between the medium's surface and the top of the moving blade, and filter through filter, discarding the first 5 ml. Using a UV spectrophotometer, the absorbance at 291 nm is measured.

RESULTS AND DISCUSSION

Preformulation studies Duloxetine HCl:

Table 7: Micromeritic properties

Parameters	Result

Research Article (ISSN: 2834-5673)

State	Amorphous powder
Odour	No characteristic odor
Colour	White colour
Solubility	Soluble in methanol and DMSO
Melting point	160°C
Bulk density	0.625 g/cc
Tapped density	0.714 g/cc
Angle of repose	39.8°
Compressibility index	18.54%
Hausner's ratio	1.14

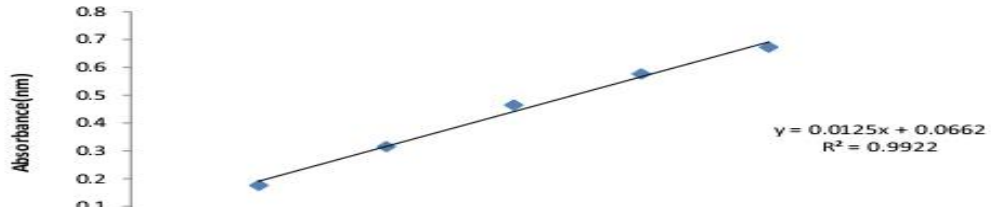
The Calibration curve of the Duloxetine HCl was characterized by determining various physical properties. The bulk density and the tapped density of Duloxetine HCl were found to be 0.625 g/cc and 0.714 g/cc respectively. The angle of repose was found to be 39.8°, compressibility index was found to be 18.54%, Hausner's ratio was found to be 1.14 revealed the fair flow properties of Duloxetine HCl. Calibration curves were constructed in pH1.2 (acidic buffer) and pH6.8 (basic buffer). And correlation coefficient values (R^2) were found to be 0.986, 0.989.

Calibration curve of Duloxetine HCl:

Table 8: Absorbance values of Duloxetine HCl at λmax 290nm (pH1.2 buffer).

Sl.no	Concentration (µg/ml)	Absorbance (290 nm)
1	10	0.177
2	20	0.316
3	30	0.465
4	40	0.576
5	50	0.672

(Figure.4)- calibration curve for DLX HCl in pH 1.2buffer

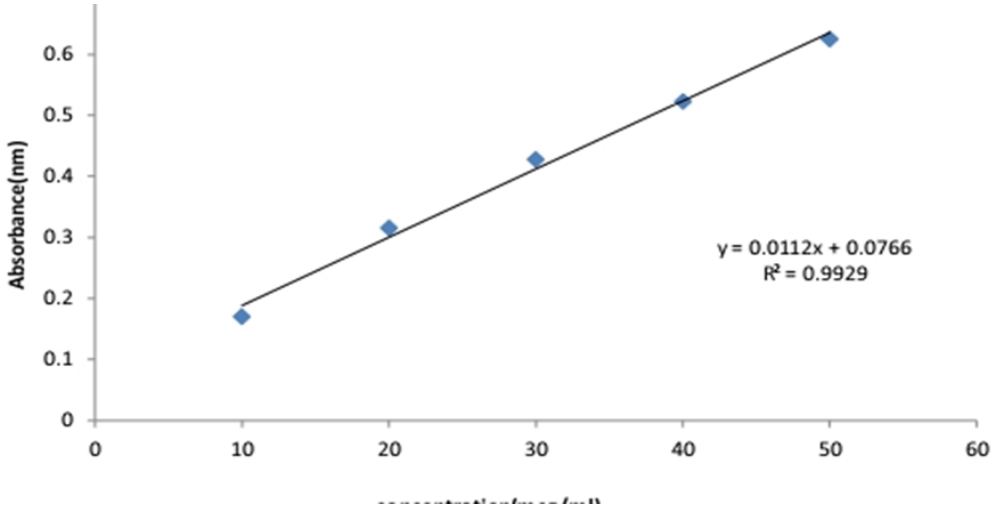


A calibration curve of DLX HCl in pH 1.2 (acidic buffer) was a plot at 290nm. Linear plot with a R^2 value of 0.9922 was obtained when absorbance value of the working standard solutions was plotted against concentration.

Table 9: Absorbance values of DLX HCl at λ_{max} 290nm (pH6.8 buffer).

Sl.no	Concentration (µg/ml)	Absorbance (290 nm)
1	10	0.170
2	20	0.315
3	30	0.427
4	40	0.523
5	50	0.625

Figure 5: Calibration curve for DL HCL in pH 6.8 buffer



A calibration curve of DLX HCl in pH 6.8 (basic buffer) was a plot at 290nm. Linear plot with a R^2 value of 0.9929 was obtained when absorbance value of the working standard solutions was plotted against concentration.

Table 10: FT-IR range for pure drug(s) (Duloxetine)

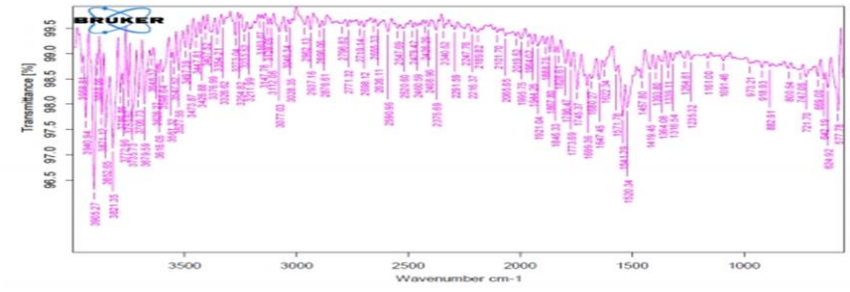
Sl. No	Functional group	Region cm^{-1}	Peak Range cm^{-1}			
			Pure drug(Duloxetine) –	DLX + HPMCP	DLX+MET+HPMCP	F445
1.	N-H	3150-3310	3273	3267.3	3175	3177.9
2.	C-H	3050-3100	3077	3062.3	3065.3	3063
3.	C=C	1450-1600	1571.2	1577.2	1569.94	1596.42
4.	C-S	1050-1400	1235	1234.9	1236.48	1236.60

The frequencies of functional groups of pure drug remained unaffected in physical mixture containing different polymers and their ingredients. Hence there was no interaction between the drug and excipients used in the study.

DRUG – EXCIPIENT Compatibility studies (Duloxetine):

FTIR STUDIES:

(FT-IR graph for pure drug of Duloxetine HCl



FTIR STUDIES:

Figure 6: FT-IR graph for pure drug of Duloxetine HCl

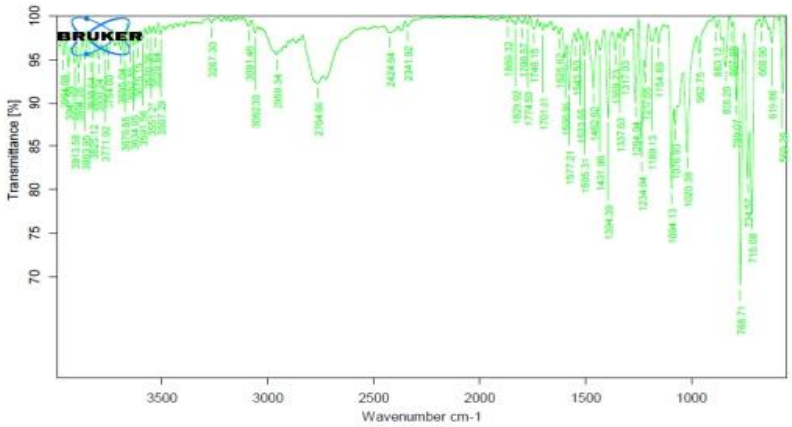


Figure 7: FT-IR graph for physical mixture of Duloxetine + HPMCP

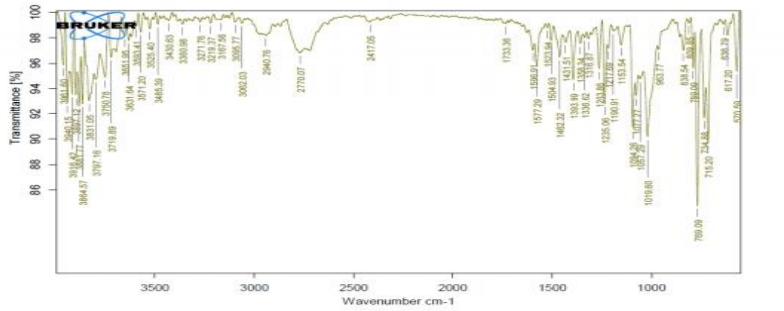


Figure 8: FT-IR graph for physical mixture of Duloxetine + SSG

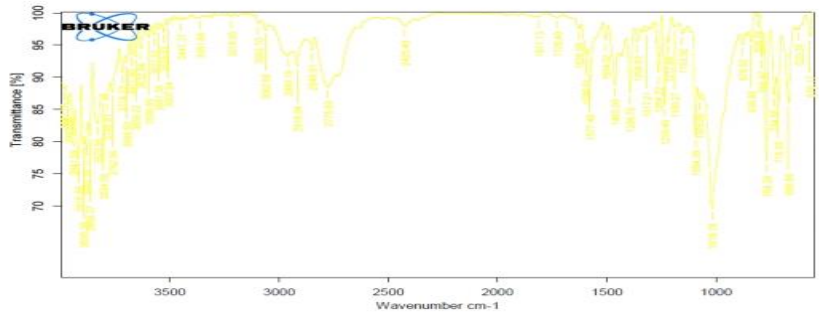


Figure 9: FT-IR graph for physical mixture of Duloxetine + Excipients

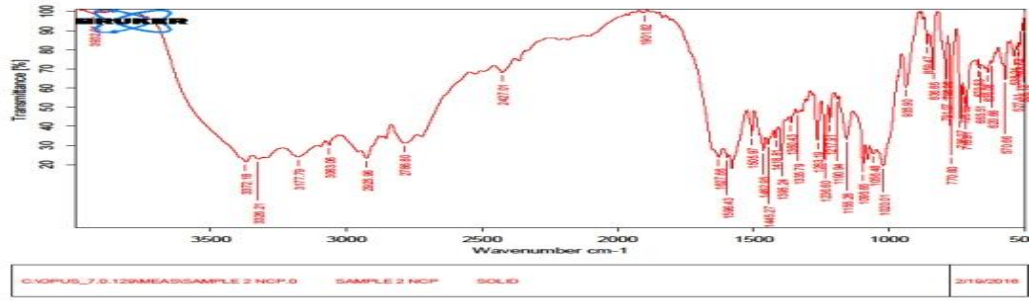


Figure 10: FT-IR graph for F445

Research Article (ISSN: 2834-5673)

Preformulation studies of Metformin

Table 11: Micromeritic properties

Parameters	Result
State	Fine powder
Odour	Characteristic
Colour	White
Solubility	Freely soluble in water as HCl salt (1.38 mg/ml)
Melting point	223 °C-226 °C
Bulk density	0.571gm/cc
Tapped density	0.251g/cc
Angle of repose	33.86 °
Compressibility index	6.15%
Hausner's ratio	1.23

The Metformin was characterized by determining various physical properties. The bulk density and the tapped density of Metformin were found to be 0.571 g/cc and 0.251 g/cc respectively. The angle of repose was found to be 33.86°, compressibility index was found to be 6.15%, Hausner's ratio was found to be 1.23 revealed the fair flow properties of Metformin. Calibration curves were constructed in pH1.2 (acidic buffer).And correlation coefficient values (R^2) was found to be 0.956.C

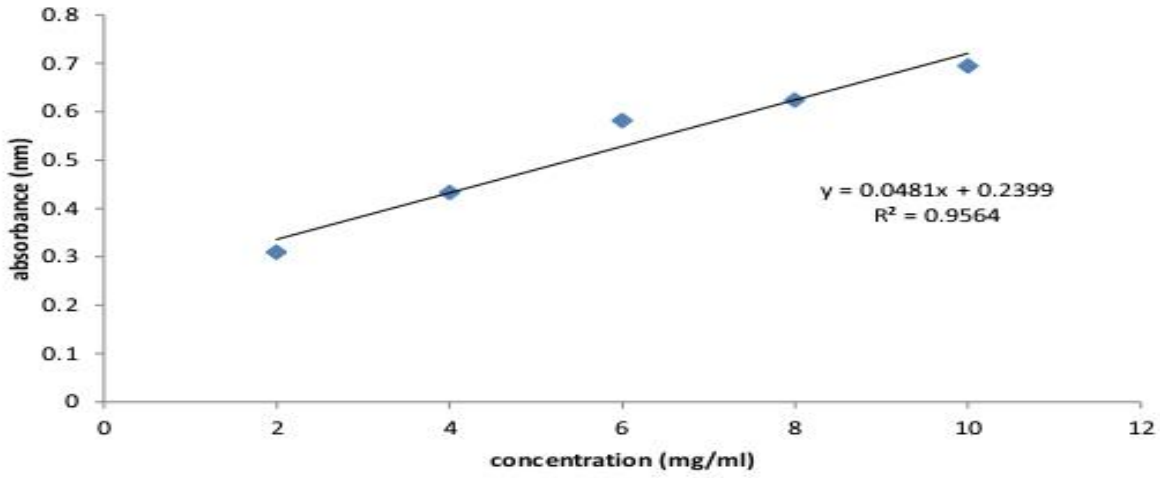
Calibration curve of Metformin:

Table 12: Absorbance values of METFORMIN at λmax 231.5nm (pH1.2 buffer).

Sl. no	Concentration (mg/ml)	Absorbance (nm)
1	2	0.309
2	4	0.433
3	6	0.581
4	8	0.624
5	10	0.694

Figure 11: Calibration curve for Metformin in pH 1.2 buffer:

Research Article (ISSN: 2834-5673)



A calibration curve of Metformin in pH 1.2 (acidic buffer) was a plot at 231.5nm. Linear plot with a R^2 value of 0.9564 was obtained when absorbance value of the working standard solutions was plotted against concentration.

Table 13: FT-IR range for pure drug (Metformin)

Sl.no	Functional group	Region cm-1	Pure-drug (metformin)	DLX + MET+ HPMCP	F445
1	N-H	3150-3310	3295	3296	3295.79
2	C-H	3050-3100	3176	3175.3	3177
3	N-CH_3	2815-2835	2964	2814.18	2786.8
4	C=N	1020-1220	1165	1166.02	1155.26

The frequencies of functional groups of pure drug remained unaffected in physical mixture containing different polymers and their ingredients. Hence there was no interaction between the drug and excipients used in the study.

DRUG – EXCIPIENT Compatibility studies(Metformin):

FT-IR Studies:

Figure 12: FT-IR graph for pure drug of Metformin

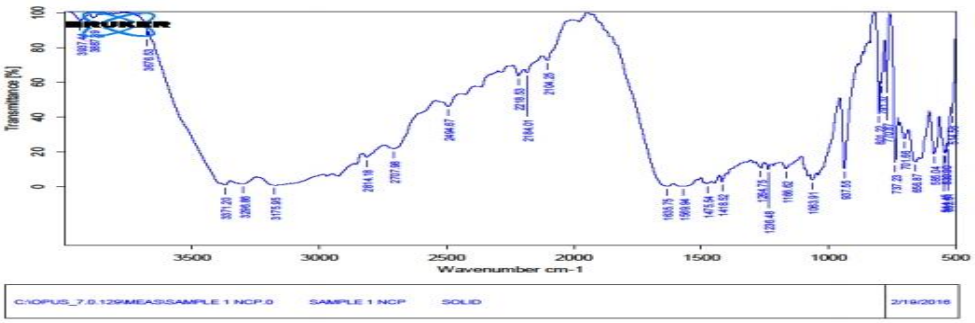


Figure 13: FT-IR graph for Duloxetine + Metformin + HPMCP

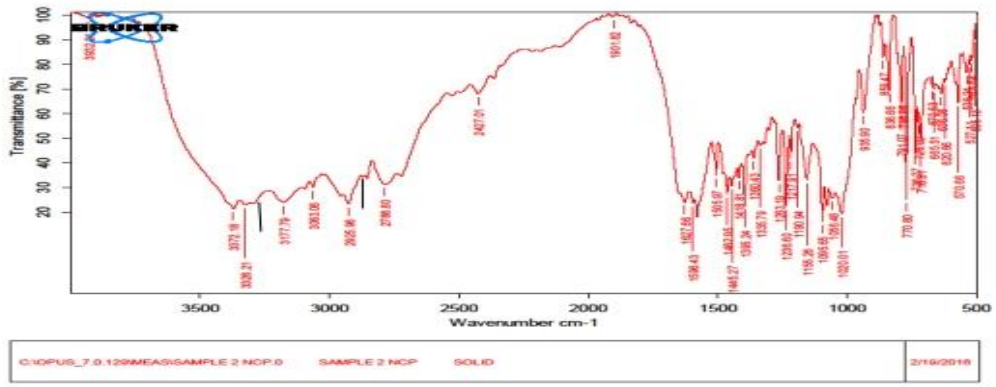


Figure 14: FT-IR graph for F445

Evaluation of tablets:

Table14: Formulation of DLX HCl core tablets

Sl.no	Materials	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)
1	Duloxetine	60	60	60	60	60
2	Sodium-starch glycolate(2-8%)	0.0	1.6	3.2	4.8	6.4
3	Magnesium stearate(1%)	0.8	0.8	0.8	0.8	0.8
4	Talc(1%)	0.8	0.8	0.8	0.8	0.8
5	Lactose (q.s.)	20	16.8	15.2	13.6	12
	Total weight	80	80	80	80	80

Evaluation of core tablets:

Table 15: Disintegration test for core tablets:

S.NO	Formulation	Time(Sec)
1	F1	72
2	F2	37
3	F3	28
4	F4	23
5	F5	17

The formulation of F4 was selected because in the above results F4 was found to be more effective regarding the quantity of the sodium starch glycolate used in it when compared to other formulations. Hence, F4 was selected and

minimized which is having 6% sodium starch glycolate as a super disintegrant.

Table 16: Formulation of press-coated tablets (DLX HCl)

SI.no	Materials	F41(mg)	F42(mg)	F43(mg)	F44(mg)	F45(mg)
1.	Core tablet(F4)	80	80	80	80	80
2.	HPMCP	0	12	18	24	30
3.	Magnesium state (1-2%)	3	3	3	3	3
4.	Talc (1-2%)	3	3	3	3	3
5.	Lactose (q.s)	214	202	196	190	184
	Total	300	300	300	300	300

Evaluation of press-coated tablets (HPMCP):

Pre-compression parameters:

Table 17: Pre-compression parameters of Duloxetine HCl press-coated tablets:

Formulation	Bulk-density (gm/cc^3)	Tapped Density (gm/cc^3)	Angle of repose (^{o})	Compressibility index (%)	Hausner's Ratio
F41	0.515 0.03	0.610 0.06	30.48 0.45	15.57 0.68	1.180 0.02
F42	0.523 0.01	0.615 0.04	31.24 0.32	14.95 0.44	1.175 0.05
F43	0.518 0.03	0.612 0.02	30.86 0.16	15.35 0.25	1.181 0.01
F44	0.517 0.02	1.613 0.08	33.28 0.74	15.66 0.15	1.185 0.09
F45	0.525 0.04	0.617 0.05	32.19 0.83	14.91 0.36	1.175 0.05

The bulk density of powder blends was found to be in the range 0.515±0.03 gm/cc³ to 0.525±0.04 gm/cc³. The tapped density of powder blends was found in the range of 0.610±0.06 to 0.617±0.05 gm/cc³. The angle of repose of powder blends was found to be in the range of 30.48±0.45 to 32.19±0.83°. The compressibility index of powder blends was found in range 14.56±0.76% to 15.66±0.15%, the Hausner's ratio of powder blends was found in the range of 1.170 to 1.185±0.09. From all the above parameters were found to be exhibited good flow properties.

Table 18: Post compression parameters of DLX HCl press-coated tablets:

Sl. No	Average weight(gms) (n=10)	Thickness (mm) (n=3)	Hardness (Kg/cm^2) (n=3)	`Friability (% (n=10)	Assay (n=2)
F41	301.2	3.5 0.04	4.65 0.07	0.42	98.10 1.55
F42	302.0	3.6 0.02	4.70 0.04	0.54	102.6 0.69
F43	298.0	3.7 0.01	4.60 0.08	0.48	102.4 1.28
F44	295.7	3.6 0.04	4.55 0.03	0.34	32.19 0.83
F45	301.0	3.7 0.02	4.75 0.06	0.65	99.80 1.46

Research Article (ISSN: 2834-5673)

The average weight of the duloxetine press-coated tablets (HPMCP) were found to be within the range of Indian Pharmacopoeia. i.e., within 7.5%. The thickness of the tablets was found to be in the range of 3.5±0.04 to 3.7±0.02Kg/cm². Uniformity thickness was obtained due to the uniform hardness which was found to be in the range of 4.55±0.02 to 4.75±0.06mm. Uniform hardness was obtained due to the equal compression force. Friability of the samples was observed to be in the range of 0.34 to0.65%. The tablets were evaluated using assay method. The drug was observed to be in the acceptable limit. The content was found to be in the range of 98.1 to 102.6%. Tablets were evaluated for the disintegration time in the IP disintegration apparatus.

Table 19: Disintegration time of press-coated tablets DLX HCl

SI . No	Formulation	Disintegration time (min)	
		P^H 1.2 buffer (120 min)	P^H 6.8 buffer (60 min)
1.	F41	1	_
2.	F42	101	_
3.	F43	115	_
4.	F44	_	6
5.	F45	_	12

Disintegration time of F41, F42, F43 was found to be within 2hrs. This claims that these formulations failed the test, as they are not supposed to be release within 2hrs. The formulations F44, F45 were disintegrated in the basic medium i.e., after 2hrs in pH 6.8 buffer. There by formulations F44, F45 qualifies the disintegration test, and F44 was considered to be the best as it disintegrates in lesser time than F45.

IN-VITRO DISSOLUTION STUDIES

Dissolution parameters: (DLX HCl)

Apparatus: USP Type II apparatus

Medium: 0.1 HCl up to 1st

2hrs, phosphate buffer(pH 6.8) remaining hours.

Sampling interval:15, 30, 60, 90 &120 min.

λmax: 291 nm, RPM: 100, Temperature: 37°C ±0.5°C

Table 20: Dissolution parameters of pH1.2 buffer

Time (min)	% of drug release				
	F41	F42	F43	F44	F45

0	0	0	0	0	0
15	8.36	5.79	2.26	0.45	0.069
30	92.0	5.98	2.91	0.94	0.091
60	95.07	6.71	3.90	2.05	0.121
90	96.2	84.91	75.4	2.99	0.326
120	97.1	94.98	86.1	3.91	0.390

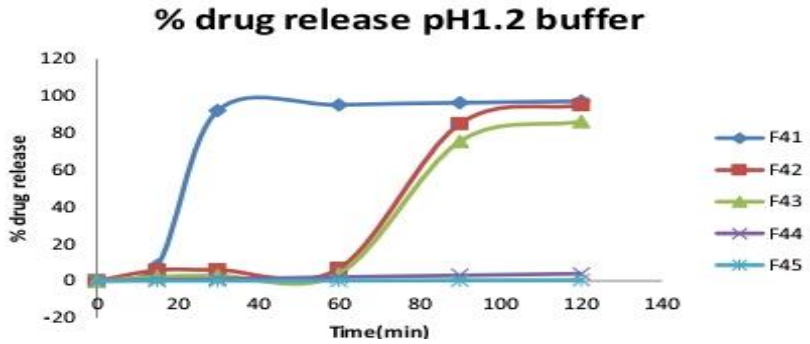


Figure 15: %drug release of F41, F42, F43, F44 & F45

Table 21: Dissolution parameters of pH6.8 phosphate buffer:

Time(min)	% of drug release	
	F44	**F45**
0	0	0
5	36.10	34.08
15	64.31	53.69
30	89.60	59.10
45	91.40	70.80
60	94.88	81.90

Figure 16: % drug release of F44 & F45

In-vitro drug release studies were conducted for the formulation using USP Type II apparatus (paddle), at100rpm. The percentage drug release at the end of 2hrs 30min was found in the range 80-93.88 %. The formulations (F44, F45) were developed to sustain the drug release from the tablet dosage form.

The drug release of formulations F44, F45 were found more than 75% of within 45min in a basic medium which is formulated by using different concentrations of HPMCP whereas other formulations release drug within 120min in an acidic medium which was formulated by using low concentrations of HPMC. Among all these formulations F44 shows better results.

Evaluation of press-coated tablets (metformin):

Table 22: Formulation of I.R. tablets of Metformine

Sl.no	Materials	F441(mg)	F442(mg)	F443(mg)	F444(mg)	F445(mg)
1	F44	300	300	300	300	300
2	Metformin	500	500	500	500	500
3	Sodium-starchglycolate	0	2.5	5	7.5	10
4	Magnesiumstearate	5	5	5	5	5
5	Talc	5	5	5	5	5
6	Lactose	10	7.5	5	2.5	0
	Total weight	820	820	820	820	820

Table 23: Pre-compression parameters of Metformin I.R tablets:

Formulation	Bulk-density (gm/cc³)	Tapped density(gm/cc³)	Angle of repose(°)	Compressibility index (%)	Hausner Ratio
F441	0.571	0.236	31.13	5.91	0.98
F442	0.521	0.249	32.16	5.96	1.11
F443	0.578	0.239	30.17	5.99	1.15
F444	0.565	0.245	31.07	6.12	1.19
F445	0.569	0.251	33.86	6.15	1.23

The bulk density of powder blends was found to be within the range 0.521 gm/cc³ to 0.578 gm/cc³. The tapped density of powder blends was found in the range of 0.236to 0.251gm/cc³. The angle of repose of powder blends was found in the range of30.17 to 33.86°. The compressibility index of powder blends was found in range 5.91% to 6.15%, the Hausner's ratio of powder blends was found in the range of 0.98 to 1.23. From all the above parameters were found to be exhibited good flow properties.

Table 24: Post-compression parameters of I.R. tablets (Metformin)

Formulation	Average weight (mg)(n=10)	Thickness (mm) (n=3)	Hardness (Kg/cm²) (n=3)	Friability (%) (n=10)	Assay (n=2)
F441	818.78	4.795	5.75	0.38	95.7
F442	819.2	5.255	5.20	0.48	96.3
F443	819.3	5.175	5.65	0.61	97.2
F444	820.2	5.150	5.30	0.39	98.1
F445	820.5	5.215	5.70	0.42	98.9

The average weight of the duloxetine press-coated (metformin tablets were found to be within the range of Indian Pharmacopoeia .i.e., within 7.5%. The thickness of the tablets was found to be in the range of 4.795 to 5.255mm. Uniformity hardness was obtained due to the uniform thickness which was found to be in the range of 5.2 to 5.75mm. Uniform hardness was obtained due to the equal compression force. Friability of the samples was observed to be in the range of 0.38 to 0.61%. The tablets were evaluated using assay method. The drug was observed to be in the acceptable limit. The content was found to be in the range of 95.7 to 98.9%. Tablets were evaluated for the disintegration time in the IP disintegration apparatus.

Table 25: Disintegration time of Metformin I.R. tablets in pH1.2 buffer

Research Article (ISSN: 2834-5673)

Sl. No	Formulation	Disintegration time (min) (p^H 1.2 buffer)
1.	F441	14
2.	F442	12.30
3.	F443	10
4.	F444	8
5.	F445	5

The disintegration time was found within range 5-14 min. The formulation F441, F442, F443, F444, F445 were disintegrated in acidic medium.

IN-VITRO DISSOLUTION STUDIES

Dissolution parameters: Metformin

Apparatus: USP Type II apparatus

Medium: 0.1N HCl buffer dissolution medium

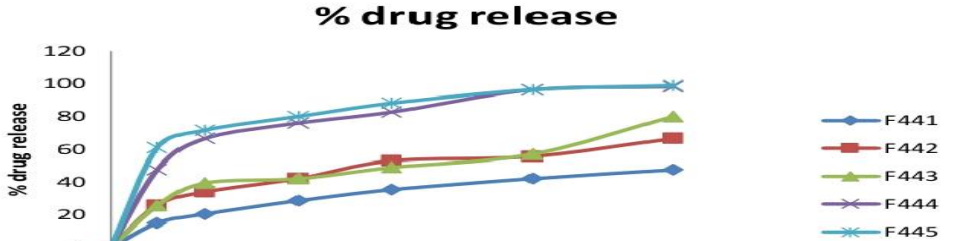
λmax : 231.5nm

RPM:50

Temperature :37±0.5°C

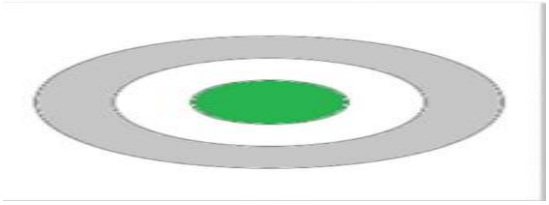
Table 26: Dissolution parameters of 0.1N HCl buffer:

Time (min)	% drug release				
	F441	**F442**	**F443**	**F444**	**F445**
0	0	0	0	0	0
5	14.91	25.76	25.47	47.45	61.01
10	20.33	33.89	39.32	66.44	71.57
20	28.47	42.033	42.03	75.93	80
30	35.254	52.88	48.81	82.71	88.13
45	42.033	55.59	56.94	96.2	96.27
60	47.457	66.44	80.00	98.1	98.8



In-vitro drug release studies were conducted for the formulation using USP dissolution apparatus Type II (paddle), at 50 rpm. The percentage drug release at the end of 60min was found in the range 76.8-99.75%. The formulations (F441, F442, F443, F444 & F445)were developed to immediate release drug. Results indicate that batch F445 shows best results in the terms of drug release.

Figure 18: Press – coated tablets enclosed within outer coat



The press-coated tablet F445 which is containing excipients which are HPMCP, sodium starch glycolate, calcium phosphate, magnesium stearate, talc.[1-49]

CONCLUSION

The purpose of the formulation of press-coated tablets of duloxetine HCl is to delay the release of drug to allow release in lower part of GIT. The reason behind the delaying of release is to prevent degradation of duloxetine HCl when it reaches to stomach. 5 different core tablets were prepared each with varying concentration of super disintegrants like sodium starch glycolate. The other excipients like dibasic calcium phosphate (diluents), magnesium stearate (lubricant), talc (glidant) were used. The prepared tablets were subjected to disintegration test at pH6.8 phosphate buffer at the disintegrated faster is selected for further enteric coating. The enteric coating was applied with the concentration of transit's time of food or dosage form stomach to jejunum of the small intestine (2hrs) as from % release Vs time plot shows the formulation F44 & F45 shows good and predictable release. Enteric coating was applied using various concentrations of HPMCP.

The formulations (F44 &F45) were developed to sustain the drug release from the tablet dosage form. The drug release of formulations F44 &F45 was found more than 75% of drug within 45 min in a basic medium which is

formulated by using different concentrations of HPMCP whereas, other formulations release drug within 120min in an acidic medium which was formulated by using low concentrations of HPMCP. Among all these formulations F44 show better results. So, the combination of 60% of HPMCP and 6% sodium starch glycolate was best for the enteric coating which has given hardness, friability, weight variation, content uniformity, percent drug release and disintegration and dissolution within officially specified limits Immediate release tablet of Metformin as promising approach to enhance the drug release profile using combination of super disintegrant. The result shows that from above dissolution study, the formulation F445 give 98.8% drug in 60min and also shows good hardness, thickness, friability.

REFERENCES

1. Cahn A, Cefalu WT. Clinical considerations for use of initial combination therapy in type 2 diabetes. Diabetes Care. 2016;39(2):S137-S145.
2. Jameshorani, M, et al. Comparative study on adding pioglitazone or sitagliptin to patients with type 2 diabetes mellitus insufficiently controlled with metformin. Open access Macedonian journal of medical sciences. 2017;5(7):955.
3. Kharroubi AT, Darwish HM. Diabetes mellitus:The epidemic of the century. World J Diabetes. 2015;6(6):850-867.
4. Ren J, et al. Hearing impairment in type 2 diabetics and patients with early diabetic nephropathy. Journal of diabetes and its complications. 2018;32(6):575-579.
5. Egan A,. Dinneen SF. What is diabetes? Medicine. 2014;42(12):679-681.
6. Guillausseau, P.-J., et al., Abnormalities in insulin secretion in type 2 diabetes mellitus. Diabetes and metabolism. 2008;34:S43-S48.
7. Holland-Carter L, et al, Impact on psychosocial outcomes of a nationally available weight management program tailored for individuals with type 2 diabetes: results of a randomized controlled trial. Journal of Diabetes and its Complications. 2017;31(5):891-897.
8. Md Rashedul Islam Rashed1 AS, Md Al Sabah3, Momin4 MM. Review of diabetes types and Care. International Journal of Current Research in Medical Sciences. 2018;4(11).
9. Lam DW, LeRoith D. The worldwide diabetes epidemic. Curr Opin Endocrinol Diabetes Obes. 2012;19(2): 93-96.
10. Sotoudeh R, Zahra Gholamnezhad Mousa-Al-Reza Hadjzadeh, Azita Aghaei. "The anti- diabetic and antioxidant effects of a combination of Commiphora mukul, Commiphora myrrha and Terminalia chebula in diabetic rats.". Avicenna journal of phytomedicine. 2019;9.5:454.
11. Harding JL, et al. Global trends in diabetes complications: a review of current evidence. Diabetologia. 2019;62(1):3-16.
12. Ghosh K, Dhillon P, Agrawal G, Prevalence and detecting spatial clustering of diabetes at the district level in India. Journal of Public Health. 2019.

13. Mathis D, Vence L, Benoist C. β-Cell death during progression to diabetes. Nature,. 2001;414(6865):792.
14. Scheen AJ. Drug treatment of non-insulin-dependent diabetes mellitus in the 1990s. Drugs. 1997;54(3):355-368.
15. Harjutsalo V, Sjöberg L, Tuomilehto J. Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study. The Lancet. 2008;371(9626):1777-1782.
16. Davies JL,et al. A genome-wide search for human type 1 diabetes susceptibility genes. Nature. 1994;371(6493):130.
17. Keenan HA, et al, Residual insulin production and pancreatic β-cell turnover after 50 years of diabetes: Joslin Medalist Study. Diabetes. 2010;59(11):2846-2853.
18. Nejentsev S, et al, Localization of type 1 diabetes susceptibility to the MHC class I genes HLA-B and HLA-A. Nature. 2007;450(7171): 887.
19. Hyttinen V, et al, Genetic liability of type 1 diabetes and the onset age among 22;650
20. Young Finnish twin pairs: a nationwide follow-up study. Diabetes. 2003;52(4):1052-1055.
21. Davis-Richardson AG, Triplett EW. A model for the role of gut bacteria in the development of autoimmunity for type 1 diabetes. Diabetologia. 2015;58(7):1386-1393.
22. Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiological reviews. 2013;93(1):137-188.
23. Kahn SE, et al, Quantification of the relationship between insulin sensitivity and β-cell function in human subjects: evidence for a hyperbolic function. Diabetes. 1993; 42(11):1663-1672.
24. McAlister FA, et al, The risk of heart failure in patients with type 2 diabetes treated with oral agent monotherapy. European journal of heart failure. 2008;10(7):703-708.
25. Rhee SY, et al, Monotherapy in Patients with Type 2 Diabetes Mellitus. Diabetes Metab J. 2017;41(5):349-356.
26. Association AD. Pharmacologic approaches to glycemic treatment. Diabetes Care. 2017;40(1):S64-S74.
27. Harper W, et al, Pharmacologic management of type 2 diabetes. Canadian Journal of Diabetes. 2013;37:S61-S68.
28. Aroda VR, et al, Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. The Journal of Clinical Endocrinology and Metabolism. 2016; 101(4):1754-1761.
29. Maruthur NM, et al, Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis. Ann Intern Med. 2016;164(11):740-751.
30. Sola D, et al, Sulfonylureas and their use in clinical practice. Arch Med Sci, 2015. 11(4):840-848.
31. Morgan CL, et al, What next after metformin? A retrospective evaluation of the outcome of second-line, glucose-lowering therapies in people with type 2 diabetes. J Clin Endocrinol Metab. 2012;97(12):4605-4612.
32. Kasznicki J, Drzewoski J. Heart failure in the diabetic population - pathophysiology, diagnosis and management. Arch Med Sci. 2014;10(3):546-556.
33. Blonde L, Dipp S, Cadena D. Combination Glucose-Lowering Therapy Plans in T2DM: Case-Based Considerations. Adv Ther. 2018;35(7):939-965.

34. Ko SH, et al, Antihyperglycemic Agent Therapy for Adult Patients with Type 2 Diabetes Mellitus 2017: A Position Statement of the Korean Diabetes Association. Diabetes Metab J. 2017; 41(5):337-348.
35. Scheen AJ, SGLT2 inhibition: efficacy and safety in type 2 diabetes treatment. Expert Opin Drug Saf, 2015;14(12):1879-1904.
36. Kaur G, et al, Ameliorative potential of Ocimum sanctum in chronic constriction injury-induced neuropathic pain in rats. Anais da Academia Brasileira de Ciências. 2015;87(1):417-429.
37. Kaur G, Jaggi AS, Singh N. Exploring the potential effect of Ocimum sanctum in vincristine-induced neuropathic pain in rats. Journal of brachial plexus and peripheral nerve injury, 2010;5(1):3.
38. Tölle TR, Challenges with current treatment of neuropathic pain. European journal of pain Supplements. 2010;4(2):161-165.
39. Quintans JS, et al, Natural Products Evaluated in Neuropathic Pain Models-A Systematic Review. Basic and clinical pharmacology and toxicology. 2014;114(6): 442-450.
40. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. The lancet. 1999;353(9168):1959-1964.
41. Dworkin RH, et al, Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain. 2007;132(3):237-251.
42. Dworkin RH, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. In Mayo Clinic Proceedings. 2010.
43. Vo T, Rice AS, Dworkin RH. Non-steroidal anti-inflammatory drugs for neuropathic pain: How do we explain continued widespread use? Pain. 2009;143(3):169-171.
44. Ngo LT, Okogun JI, Folk WR. 21st century natural product research and drug development and traditional medicines. Natural product reports. 2013;30(4):584-592.
45. Butler MS. Natural products to drugs: natural product-derived compounds in clinical trials. Natural product reports. 2008;25(3):475-516.
46. Li, J.W.-H. and J.C. Vederas, Drug discovery and natural products: end of an era or an endless frontier? Science. 2009;325(5937):161-165.
47. Gangadhar M, et al, Future directions in the treatment of neuropathic pain: A review on various therapeutic targets. CNS and Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS and Neurological Disorders). 2014;13(1):63-81.
48. Dworkin RH. Turk DC. Accelerating the development of improved analgesic treatments: the ACTION public–private partnership. Pain Medicine. 2011;12(s3).
49. Tesfaye S, et al, Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"–a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. PAIN®. 2013;154(12):2616-2625.