A Review on Diabetic Neuropathy and Development of Sustained Release Tablet Containing 'Epalrestat'

A Project Submitted

by

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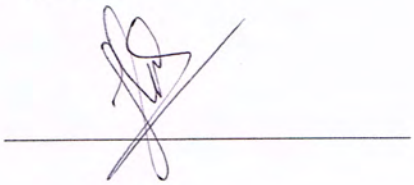
Dedicated to my Parents

Certification Statement

This is to certify that the project titled "A Review on Diabetic Neuropathy and Development of Sustained Release Tablet Containing Epalrestat" submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy, from the Department of Pharmacy, BRAC University constitutes my own work under the supervision of Dr Mesbah Talukder, Associate Professor, Department of Pharmacy, BRAC University. Throughout the project, I have given appropriate credit where I have used the language, ideas or writings of another.

Signed



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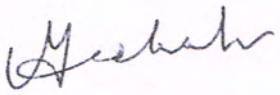

Acknowledgement

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Abstract

Pain is a common sensation which associates distressing feeling, often caused by intense or damaging stimuli.. But if pain gets into nerves with a tingling, shooting sensation or like an electrical flow of current in nerve pathways then it becomes an exceptional term which is more difficult to explain or tolerate and known as ‘Diabetic Neuropathy’ (DN) complication caused by long term Diabetic condition. In accordance to the patient comorbidities and pain phenotype treatment for DN should be advised. In the context of treatment, a new addition here is Epalrestat drug whose (Epalrestat 50mg) efficacy and safety have been established by clinical trials, however compliance still remains to be a challenge. This review holds a detailed glimpse of DN and stands to design and assess a sustained release dosage form of Epalrestat in order to attain prolonged therapeutic effect with minimum side effects against this neuropathic complication.

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List of Acronyms

DM = Diabetic Mellitus

NIDDM = Non-Insulin Dependent Diabetes Mellitus

IDDM = Insulin Dependent Diabetes Mellitus

DN = Diabetes Neuropathy

DPN = Diabetic Peripheral Neuropathy

DSPN = Distal Symmetric Polyneuropathy

ARI = Aldose Reductase Enzyme

NADPH = Nicotinamide Adenine Dinucleotide Phosphate

1. Introduction

1.1 Diabetes

Diabetes is a chronic disease condition, which can generate few metabolic diseases; such a disease condition can also be regarded as hyperglycemia resulting from defective insulin secretion or can also be concomitant with increased cellular resistance towards insulin or both. This disease condition can be classified into two types generally. Categorized by Type I Diabetes Mellitus or IDDM and Type II Diabetes Mellitus or NIDDM. The type II is the most known type of diabetes mellitus; can be characterized by hyperglycemia, relative insulin deficiency and insulin resistance. (Abdulfatai B. Olokoba, Olusegun A. Obateru, 2012) A new known as IFG or Impaired Fasting Glucose defines the data on glucose values that are greater than or equal to 100mg/dL and upto 125mg/dL. (Harikumar et al., 2014)

Such chronic hyperglycemic and metabolic disturbances may lead to long term organ and tissue damage along with their dysfunctional behavior which involves especially nerves and blood vessels. Diabetes has become a growing public health problem worldwide. It is also currently a prominent cause of disability and death worldwide. (Akter, Rahman, Abe, & Sultana, 2014) The socioeconomic burden which has been posed by this disease is enormous due to its spectrum of complications which may range from peripheral vascular disease (PVD) to coronary artery disease (CAD) to chronic kidney disease (CKD) to blindness etc. (Rao & Vv, n.d.)

1.1.1 Statistical Analysis of Diabetes

Particularly affected regions are Eastern pacific and Asia. In a worldwide view a study of 2011 found that, China carried largest number adults with diabetes (9% of the population or around 90 million), India (8% of the population or around 61.3 million), Bangladesh (10% of total population or around 8.4 million). (Akter et al., 2014)

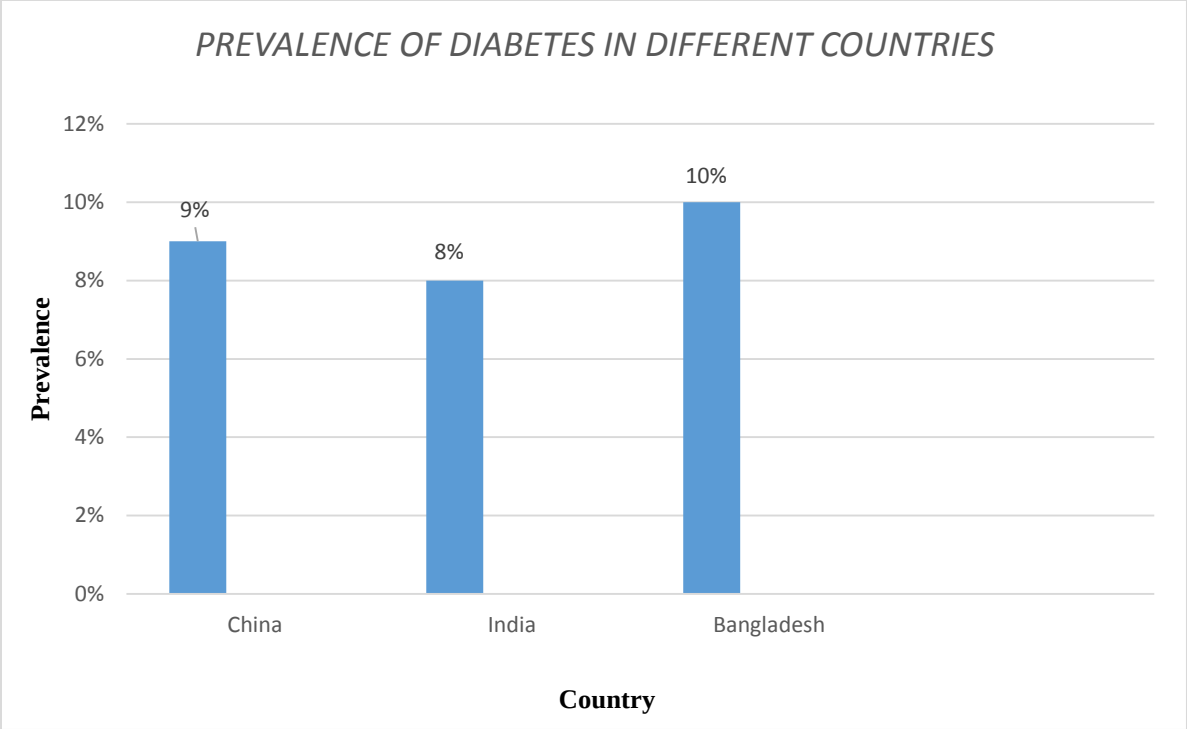

Figure 1.1.1(a): Statistical Analysis of Diabetes

Anthropometric data and the data on blood glucose level of 7541 adults who were aged 35 years or more were collected from the biomarker sample of year 2011 Bangladesh Demographic and Health Survey (a national representative survey with a multistage, cluster and stratified sampling design). In this survey the inclusive prevalence of pre-diabetes was 22.4% and diabetes was 9.7%. Amongst the urban or inner city residents' prevalence of diabetes was found nearly 15.3% when compared with 8.3% among rural or countryside residents. Thus, overall it appears that, 56.0% were unaware that they had such a disease condition and on the other side, only 39.50% were aware and thus receiving treatment accordingly. The study also found that probability of diabetes in individual who were aged 55 to 59 years was almost two times that in those who were aged between 35 to 39 years. (Akter et al., 2014) Lastly, it stands that almost two in twenty adults of this country was found to be suffering from diabetes. Thus, better detection, awareness, prevention and treatment should be adapted as urgent action in this country.

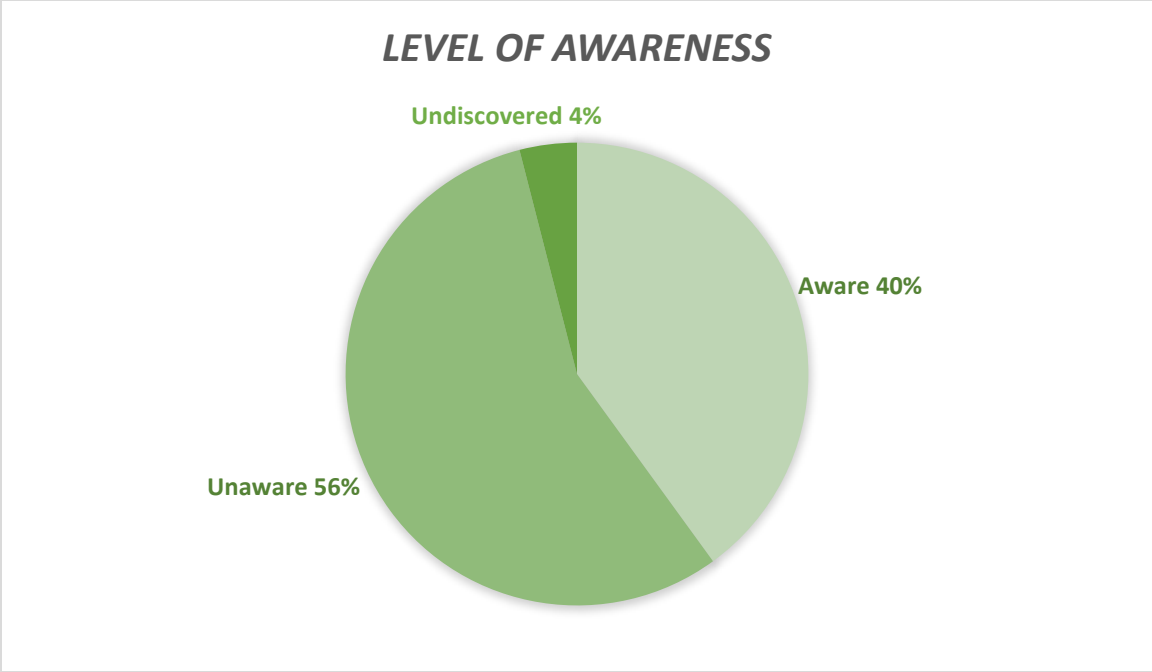

Figure 1.1.1(b): Statistical Analysis of "Diabetic Condition" Awareness Among Individuals

1.1.2 Prevalence Rate Variable Factors

Prevalence of Pre-Diabetes and Diabetes varies upon various factors. Such as-

a. Individual's Age

b. Body Weight

c. Educational Qualification

d. Socioeconomic Status

e. Hypertensive Patients

f. Region of Habitation

1.2 Diabetic Neuropathy

Diabetic neuropathy refers to a painful complication resulting from diabetes that can lead to effect numerous aspects or activity of daily life and may relentlessly limit individuals' daily regular functions. (Huizinga & Peltier, 2007) It is a serious, painful, prevalent and polymorphic complication of diabetes mellitus. Reflects the presence of symptoms and various signs of `Peripheral Nerve Dysfunction` in 50% patients who had diabetic condition for more than 25 years. According to a study report in Finland shows neuropathic prevalence in 8.3% people who were newly diagnosed with type II diabetes. (Huizinga & Peltier, 2007) Characterization can be done by identifying tingling or shooting pain, numbness or sensation of electrical current flow in nerves sort of of symptoms. Patients who maintains long-term admirable glycemic control may reduce their lifetime incidence of diabetic neuropathy up to 20%.

1.2.1 Types of Diabetic Neuropathy Pain

Diabetic neuropathic pain can be classified into two types generally. Those are-

a. *Acute Sensory Neuropathy*- It refers to acute or sub-acute onset of severe and frequent discomfort devoid of any associated signs. May gradually decrease over time as euglycemia is acquired.

b. *Chronic Sensorimotor Neuropathy*- A long term complication arising from diabetes accompanying with clinical signs of neuropathy and symptomatic pain. Our project work of finding a better treatment option intends to focus on this neuropathic pain mainly. (Huizinga & Peltier, 2007)

1.2.2 Statistical Analysis of Diabetic Neuropathy

With the purpose to assess the incidence of Diabetic Peripheral Neuropathy a study was conducted in Bangladesh (Birdem Hospital), with 294 diabetic outpatients in which 139 were men, and 155 were women. The overall prevalence was found to be 19.7% suffering from diabetic neuropathy, which involved 20.9% male and 18.7% female. (Morkrid, 2010)

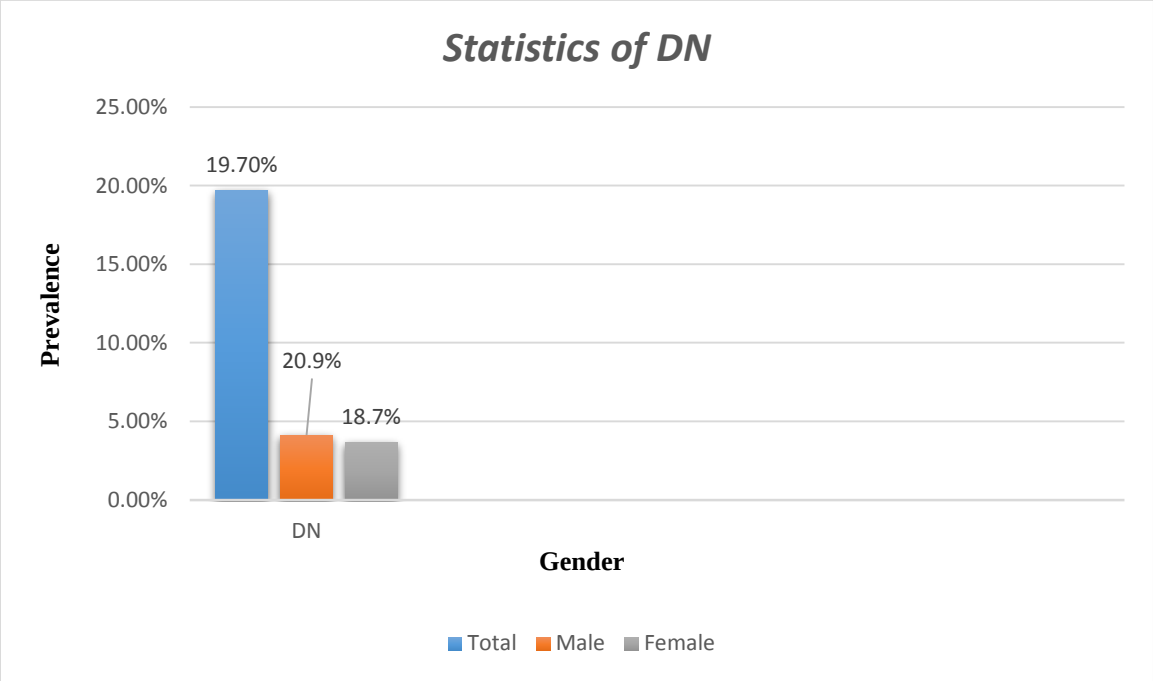

Figure 1.2.2: Statistical Analysis of DN

1.2.3 Prevalence Rate Variable Factors

Most Diabetic patient from a specific aging view will have Diabetic Neuropathy. But the prevalence rate of diabetic neuropathy varies in accordance to-

a. Increasing Age

b. Socioeconomic Prominence

c. Insulin Treatment

d. Long Duration of Diabetes

e. Higher HbA1c

The first 3 are statistically significant factors prior to risk, whereas the glycemic control and long duration of diabetic condition are doubtful statistical risk variables for diabetic peripheral neuropathy. The survey conducted on 2011 found that the performance of focuses of diabetic neuropathy was worse on all the functional tests associated with lower leg and especially for the balance and protective sensational test. They are at high risk of developing foot related problems as an outcome of this chronic condition. (Morkrid, 2010)

1.2.4 Diagnosis

Peripheral neuropathy consists many probable causes, thus beside a physical performance related exam which may also comprise blood tests, analysis or diagnosis of such a chronic condition may also require-

a. Full medical history

b. Neurological examination

c. Imaging tests

d. Nerve function tests

e. Nerve biopsy

f. Skin biopsy

1.2.5 Management

Diabetic Neuropathic pain can often be chronic, debilitating and frustrating. Such pain is tough to treat and patient hardly can achieve complete relief from pain. Thus there are no such treatment which will suppress the painful complication completely, as result prevention remains to be the best strategic choice. (Huizinga & Peltier, 2007)

1.2.6 Prevention

Single ultimate prevention relevant measure for diabetic neuropathy would be Glycemic control. Moreover, controlling hypertension and hyperlipidemia, taking aspirin in a scheduled manner, consumption of alcohol in a balanced way, ceasing smoking, following a balanced diet may also provide pleasant result against neuropathic pain. (Huizinga & Peltier, 2007)

1.2.7 Treatment

In the context of treatment prior to `symptomatic treatment` of such a disease condition mainly include medicines in order to relieve pain primarily. Such as-

a. Pain relievers

b. Anti-seizure medications

c. Antidepressants

d. Topical treatment

There are few more alternative options for medicines. Such as-

a. Acupuncture

b. Alpha-lipoic acid

c. Herbs

d. Amino acids

Specifically, about therapies-

a. Transcutaneous electrical nerve stimulation

b. Physical therapy

c. Surgery

Few modifications in lifestyle and home remedies like Feet care, Exercise, Quit smoking, Healthy diet, Avoiding Excessive consumption of Alcohol, Regular or scheduled monitoring of blood glucose level may also bring temporarily satisfactory outcome.

1.3 Epalrestat

A new addition to such field of treatment is Aldose Reductase Enzyme Inhibitor drug. A current addition to such type of drug agent includes Epalrestat drug.

Epalrestat is a noncompetitive, reversible aldose reductase inhibitor. It works on inhibiting the accumulation of intracellular sorbitol, which is basically known to be the major cause of Diabetic Neuropathy, Retinopathy and Nephropathy. It inhibits the enzyme with minimum possible side effects and thus known to be a highly effective and safe agent for diabetic neuropathy treatment.

Generally dosing schedule of such a medicine involves an oral dose of 50mg thrice per day and it is an immediate release (IR) designed dosage form. (Shende, Baig, & Doifode, 2018)

1.4 Project Purpose

The purpose of this project is to find or formulate a better treatment option of painful Diabetic Neuropathy from an existing option. To be more specific focusing on the development and assessment of a sustained release tablet or dosage form of Epalrestat for a better medication option in Diabetic Neuropathy. Because Sustained release dosage forms currently has obtained wide level of acceptance over conventional term of dosage forms in order to treat acute or chronic severity of various disease conditions. Such a dosage form or system provides prolonged duration of drug delivery as well as long duration of action along with implying predictability and reproducibility of the release kinetics of drug. To add on, for better patient compliance they also work on reducing the incidence and severity of relevant side effects.

1.5 Future work

I am moving forward with the lab work primarily intending to validate a proper method or procedure of forming Epalrestat tablet with its assigned ingredients. After few trials I have come up with a granulation procedure through which I am able to compress tablets appropriately with desirably designed various formulas for further evaluation on its` effectiveness, so that a better formulation can be developed having more effective release pattern of therapeutic significance.

I have prepared a Standard Curve using the active pharmaceutical ingredient of this drug.

Further work will be on formulating tablets with each newly designed different formulas and evaluation of their safety, efficacy and therapeutic effect; mainly on evaluating their release pattern and efficiency based on the desired outcome.

2. Materials & Methodology

2.1 Materials

For the purpose of developing a modified dosage form of Epalrestat the ingredients involved are listed below with their properties.

2.1.1 Polyvinyl Pyrrolidone

A polymer well soluble in water prepared from monomer N-vinylpyrrolidone. As an ingredient, it is used for binding property or as a binder. In the construction or formulation of solid oral dosage forms tablet binders are used in order to hold the pharmaceutical active ingredient together in a cohesive mixture or mix. Although binder products are usually differentiated based on the manufacturing process involved. Binders, which are used for wet granulation process, are hydrophilic in nature and soluble in water. Usually dissolved in water in order to form a wet mass which is then granulated for further method.

Here Polyvinyl-pyrrolidone is used for such purpose as binder. Also known as Povidone or PVP.

By appearance it can be appeared as white to light yellow, hygroscopic amorphous powder. It shows solubility in polar solvents as well such as various alcohols. When it is dry, it carries a flaky light hygroscopic powder, which is freely absorbed up to 40% of its overall weight in the existing atmospheric media or specifically water. (Rowe, Sheskey, & Owen, n.d.)

PVP when mixed with iodine, a complex formation occurs known as povidone iodine. Such complex possesses disinfectant characteristics. This kind of complex chemical is used for solutions, liquid soap, ointment and surgical scrubs. It is equally effective as Talc because of its pleurodesis properties. It can be also used as stabilizing agent in all inorganic solar cells.

FDA has approved this chemical for several uses and declared or assured its safe use.

Figure 2.1.1: Polyvinyl Pyrrolidone

2.1.2 Polyethylene Oxide

It can be castoff widely as tablet binder at 5-85% of concentrations in the formulation of tablets. It is known as a nonionic homopolymer which is of ethylene oxide. It can be signified as (CH2CH2O)*n*, and here 'n' symbolizes the average number of oxyethylene groups. The high molecular weight grades generate delayed release of drug. By appearance it seems to be off-white to white powder with free flowing characteristics, which has a slight ammoniacal smell. With strong oxidizing agents it shows incompatibility. (Rowe et al., n.d.)

This chemical is prepared from ethylene oxide polymerization with the presence of appropriate catalyst.

It is also known for its excellent mucoadhesive polymer. Low levels of such chemical is used as effective thickeners. It is counted in the "FDA Inactive Ingredients Guide". Animal studies show low levels of toxicity irrespective of the route of administration implemented.

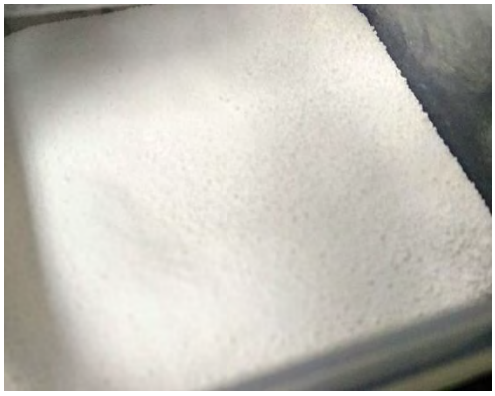

Figure 2.1.2: Polyethylene Oxide

2.1.3 Microcrystalline Cellulose

In this wet granulation method, microcrystalline cellulose is used as disintegrant. According to that specific nature, this chemical helps tablet to disintegrate and release their medicinal substances when it is in contact with moisture. So basically disintegrants helps tablet to break down after oral administration. It refers to a depolymerized cellulose that appears with a tasteless, whitish, fragrance-free, crystalline powder appearance. Such a chemical is accessible in altered particle sizes along with moisture grades. Incompatible in contact with strong oxidizing agents.

This excipient is manufactured from control hydrolysis (mineral) acidic solutions alpha cellulose, which is acquired from fibrous natured plant materials as pulp. Subsequent to the hydrolysis, hydrocellulose is sterilized or purified through filtration. Then the aqueous slurry is put under spray-dried facility in order to form porous dry particles. (Rowe et al., n.d.)

Microcrystalline cellulose is generally considered as a comparatively non-toxic and non-irritant chemical. Because it cannot be absorbed systematically and thus has little toxic potency. Large quantities of cellulose may cause laxative effect, but not known to be very harmful when used in pharmaceuticals as excipients. Thus, this chemical is quite safe to be used.

Figure 2.1.3: Microcrystalline Cellulose

2.1.4 Colloidal Silicon Dioxide

Colloidal silicon dioxide is used here to improve the flow ability of formulation or in other words as a glidant. A chemical posing glidant property will only function at a certain range of concentrations. In fact, above this certain concentration this chemical might work to inhibit the flow ability. Thus in pharmaceutical manufacturing or to be more specific tablet manufacturing glidant is used just prior to compression. It is a submicroscopic silica. It appears to be bluish-white colored, odorless and a non-gritty amorphous powder. (Rowe et al., n.d.)

According to its preparation method, vapor hydrolysis of chlorosilanes are used along with hydrogen-oxygen flame.

It basically works on correcting the surface irregularity, decreasing surface change and reducing interparticular friction. This results in a decrease in angle of repose thus indicating enhanced powder flow ability.

Colloidal silicon dioxide is also used as stabilizing agent, as thickeners and suspending agent. It is broadly used in topical and oral preparations; observed safe as nonirritant and nontoxic excipient. Although subcutaneous or intraperitoneal injection may cause local tissue reactions. Therefore, should be administered parentally.

Figure 2.1.4: Colloidal Silicon Dioxide

2.1.5 Talc

Talc is used here in this formulation as a lubricant. This organic chemical was used to reduce the friction among surfaces when comes in mutual contact. This eventually leads to reduce the generation of heat when the surface moves. It may also transmit forces. It is a very fine, grayish-white, impalpable, odorless crystalline powder in term of appearance. It is not compatible with quaternary ammonium compounds. (Rowe et al., n.d.)

Talc may also be used as glidant or diluent in pharmaceutical manufacturing field. This is also adequately used as a dissolution retardant in the development of sustained release or controlled release products. It is a stable and firm material; can be easily purified or sterilized through heating at certain temperature.

Talc is known to be a natural product. Thus consists of microorganisms. So after sterilization it can be regarded safe for using as lubricant.

Figure 2.1.5: Talc

2.1.6 Dicalcium Phosphate

Also well recognized as dibasic calcium phosphate in the USP. Here in this formulation designing method is used as diluent or to be more specific as dilutant or as a filler as well. When fluids are way too viscous it becomes difficult to be pumped, thus may be problematic during transportation in such state. Here the diluents or fillers may inhibit the excess viscosity of fluids. It appears like a whitish powder without any odor or taste. It occurs similar as triclinic crystals.

Such chemical can be prepared from reaction of pure phosphoric acid and calcium hydroxide which is from limestone basically in aqueous suspension within stoichiometric ratio. Such procedure may also be alternative with spray drying process. Dicalcium phosphate shows incompatibility with certain tetracycline antibiotics. (Rowe et al., n.d.)

Dicalcium phosphate can also be used in nutritional supplements as a source of calcium apart from being an excipient. The mechanism of predominant deformation of this chemical's coarse-grade is brittle fracture. This inhibits the strain rate sensitivity of the study material which eventually allows easy transportation from lab to production area or scale. This chemical is widely regarded as a nontoxic, non-irrirtant and safe excipient option for food, oral pharmaceutical products and in toothpaste preparations as well.

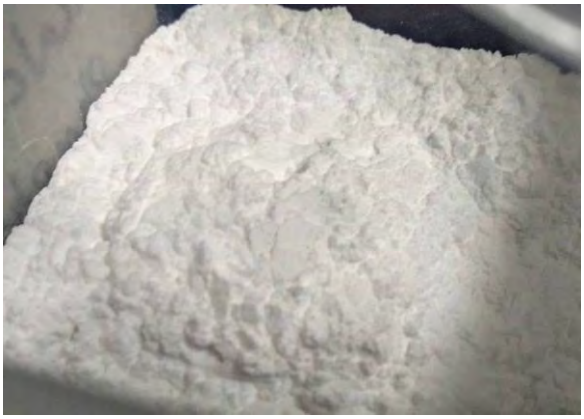

Figure 2.1.6: Dicalcium Phosphate

2.1.7 Methocel K4M CR

Methocel are soluble in water and such polymers are generated from cellulose. This can also be known as cellulose ethers. Here Methocel polymers are used as SR polymers and hydrophilic is aspect of nature. Such a product can also be beneficial as binders, thickeners and also as film formers. In accordance to the formulation of a hydrophilic matrix, which may provide a modified mechanism for extended or sustained release for oral dosage form, here Methocel polymers or cellulose may contribute in meeting the requirements of desirable drug solubility needs. Appears with a whitish and odorless appearance.

Methocel K4M CR polymers provide modified capability of method for modified release activity of matrix formulation and may also deliver exceptional flow properties of that formulation. Thus by using Methocel the optimum properties for a desired formulation can be obtained.

Such chemical is regarded safe by the FDA, therefore broadly used in drug and food industries.

Figure 2.1.7: Methocel K4M CR

2.1.8 Ethocel 7 cps

In this experiment Ethocel polymer provides binding properties to the formulation. Such polymers are inert physiologically. There are nine different types of polymer with a broad range of viscosity and different molecular weights in this class of Ethocel for numerous pharmaceutical applications. By appearance, it is whitish, odorless and tasteless in nature.

With a good adhesive property, Ethocel forms a strong hard film around tablets. Such polymers can also be an option for different diffusible barrier and whose properties can be modified or designed by solvents used, viscosity, choice of plasticizer and pore forming water-soluble additives as well.

Such a polymer used in this experiment may also contribute in the modified release action of drug or particularly in Epalrestat.

Figure 2.1.8: Ethocel 7 cps

2.2 Methodology

2.2.1 Methodology of Research

To obtain all necessary valid information that are mentioned in this review paper literature review was done. Thus, information were collected from numerous credible sources, along with different journal articles, review articles, online scholarly database and books. The journals which were searched extensively throughout this preparation are listed below-

a. Handbook of Pharmaceutical Ingredients

b. International Journal of Diabetes in Developing Countries

c. Annals of Neurology

d. World Journal of Diabetes

e. Diabetes and Age Related Complications

f. Journal of Clinical and Diagnostic Research

g. Neuroendocrinology

h. Oman Medical Journal

i. Frontiers in Neurology

j. F1000Research

k. Bulletin of the World Health Organization

The aim of this paper is to review all information regarding Diabetic Neuropathy along with its frequency level from valid sources over the past few years. This also includes the design and assessment of a better treatment alternative against Diabetic Neuropathy related complications.

From here onwards, starts lab work that are completed to some extent and further work will be conducted later.

2.2.2 Standard Curve

With samples of known properties, which are the standards a graph was plotted known as standard curve. Here with the active pharmaceutical ingredient of Epalrestat and solvent methanol a standard curve was prepared.

a. Accurately weighed drug was dissolved in Methanol.

b. Stock solution with assigned concentration was prepared.

c. Absorbance was taken with concentration of 1, 3, 5, 8, 10 µg/ml in UV-visible spectroscopy in the wavelength of particularly 367 nm.

d. Data of concentration and absorbance were plotted in the graph to obtain a standard curve.

Concentration	**Absorbance**
1	0.086
3	0.256
5	0.35
8	0.655
10	0.843

Table 1.1: Concentration & Absorbance Taken From UV-visible Spectroscopy (367nm)

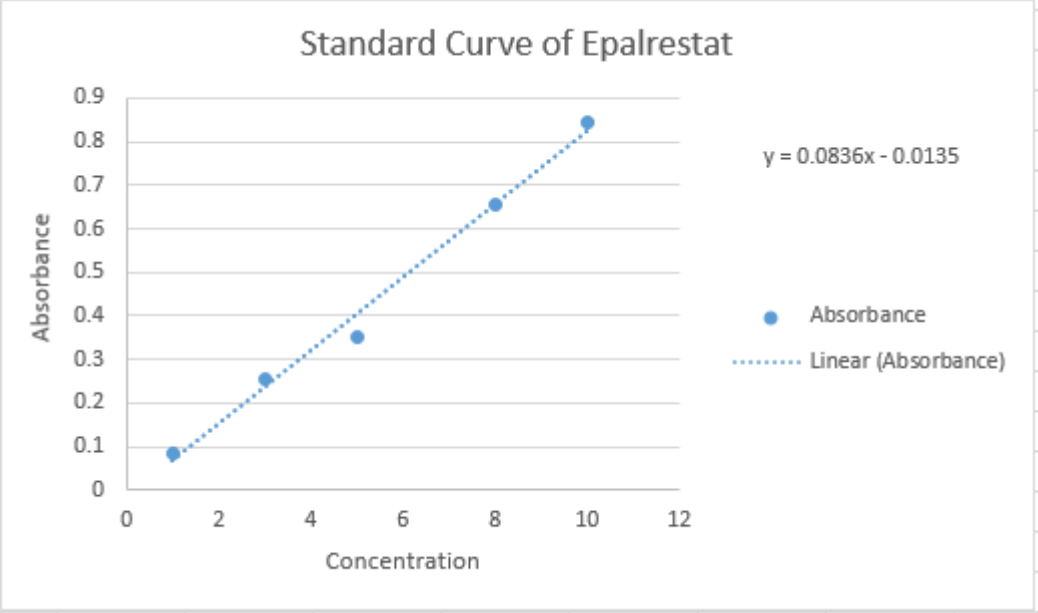

Figure 2.2.2: Standard Curve of Epalrestat

In the next step I have validated the Method.

2.2.3 Method Optimization

In this particular step I have identified the exact procedure of preparing tablets with assigned materials or ingredients. Here I have observed which ingredient when, how and in what quantity should be added in the formulation to form a perfect tablet. I have proceeded with wet granulation procedure, the temperature of 60℃ and a mesh size of 30 made a desirable outcome in this experiment in the method optimization. On the 9th trial tablets were formed with ideal appearance following few basic techniques.

Figure 2.2.3: Tablets Formed in Lab during Method Optimization

In future work specifically I will have to prepare tablets with 5 different formulas assigned with differences in ingredients quantity and evaluate their various parameter in order to assess their effectiveness.

2.2.4 Evaluation of Pre-Compression Parameters of Dry Blend Powders

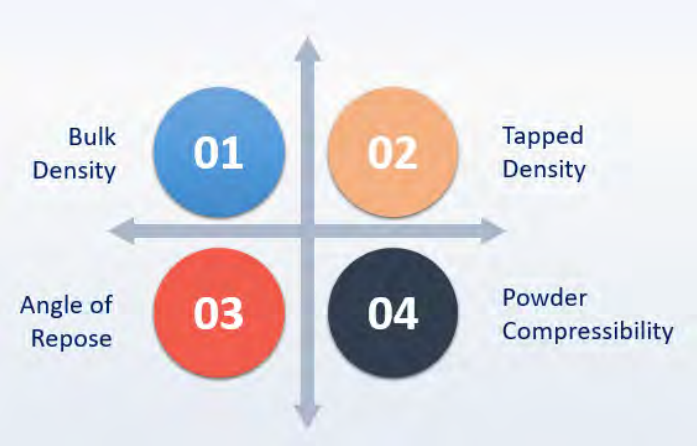

Figure 2.2.4: Pre-Compression Parameters of Dry Blend Powders

Bulk Density-

Bulk density basically refers to the mass of many particles of sample material divided by the total volume they occupy. Thus it is the quotient of weight to the sample volume. The unit is 'g/cm^3'.

Tapped Density-

Tapped density is the bulk density of powder after a specified compaction which usually involves vibration in container. So in short it is the quotient of mass of the sample to the tapped volume. Usually expressed with 'g/cm^3'.

Angle of Repose-

In loose powder the friction force can be measured by the angle of repose (θ). So it is the angle (relative to horizontal base) at the conical pile which is shaped when a granular material is poured on to a horizontal surface.

Powder Compressibility-

It is designated as the test to characterize and analyze powder flow properties. Here compressibility index and Hausner's ratio deals with observing the flow pattern of powder before compression. Thus it stands for the relative importance of inter particulate interfaces among powder.

2.2.5 Evaluation of the Tablets formed

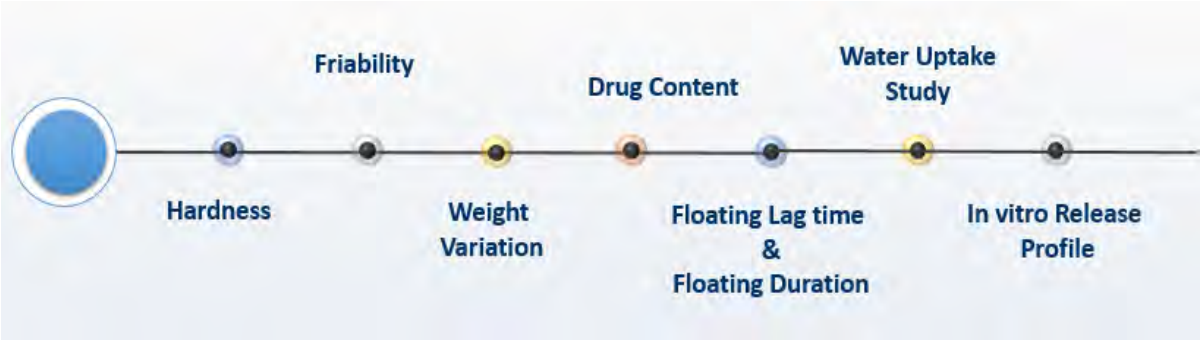

Figure 2.2.5: Parameters of Tablets Formed

Hardness Test-

Indicates and represents the capability of powder to withstand mechanical shock during transportation or shelf life. Expressed with 'kg/cm^2".

Friability Test-

It involves a tumbling apparatus which revolves in 25rpm for 4 minutes. Then the tablets weight is compared to the previous one in order to identify the percentage loss during this test.

Weight Variation Test-

It is known to measure the percentage deviation from average weight. There are few standard limit values in such test.

Drug Content-

Here certain amount of tablets is weighed first; then powdered; specific weighed amount is dissolved in solvent for further dilutions; then with absorbance and concentration found in UV-visible spectroscopy, standard curve was established.

Floating Lag Time and Duration-

This test identifies the time required by particular sample tablets to emerge at the surface when comes in contact with dissolution medium and also the duration for which it remained buoyant.

Water Uptake Study-

This test requires 8 hours. It refers to the swelling of polymers measurement by their ability in absorbing water and swell.

In Vitro Release Profile-

This test requires minimum 12 hours. It determines release of prepared tablets in dissolution medium upto 12 hours. Then sample withdrawn at known time interval should be replaced, on the other hand sample analysis should be done spectrometrically. This provides the result of percent cumulative drug released.

This is how my project will proceed throughout the assessment study in order to obtain a drug (containing Epalrestat) of sustained, prolonged release in the treatment of Diabetic Neuropathy.

3. Discussion

3.1 Diabetic Neuropathy

Over the last few centuries, worldwide changes in lifestyle has led to in a huge increase in the occurrence or frequency of diabetes. Neuropathy is a serious and painful complication of the type I and type II diabetes both. According to an estimation, the prevalence of neuropathy was found in 8% of newly diagnosed patients and more than 50% of patients with long lasting disease condition. (Deli, Bosnyak, Pusch, Komoly, & Feher, 2013) Can be characterized by burning, shooting, lancinating, tingling, and sharp or even may appear like electrical shock sensation. This can vary from moderate to severe level depending on individual. Such unpleasant sensations can be constant and may gradually affect the quality of life of individuals by putting impact on their performances in daily activities. No exact theory of pathogenesis for such a condition has yet been established instead several theories have been proposed. (Schreiber A , Nones C, Reis R, Chichorro J, 2015) With accuracy Diabetic Neuropathy can be defined as, "a distal, symmetrical or progressive degeneration of sensorimotor and autonomic peripheral fibers, which are attributable to microvascular and metabolic changes as an outcome of the consequence of chronic hyperglycemic and various cardiovascular relevant risk factors". (Rolim, da Silva, De Sá, & Dib, 2017)

According to a study report, among all PDN patients, 39% have never received for this complication, while on the other hand 12.5% had never even reported their symptoms to health practitioners. (Rolim et al., 2017)

Among the two types of diabetic neuropathy, Autonomic neuropathy contributes to malignant arrhythmia, myocardial infarction and sudden death; sensorimotor neuropathy can be recognized by paresthesia, pain or sensory loss. This project is to focus on the treatment of sensorimotor neuropathy. (Deli et al., 2013) Generally, treatment for such types of diabetic neuropathy is recommended in accordance to PDN treatment guidelines and drugs selection should be based on patient comorbidities.

3.1.1 Mechanism of Diabetic Neuropathy

The primary cause of diabetic neuropathy would be some metabolic disorders. Due to insulin deficiency or resistance, hyperglycemia is induced and enhances the Polyol Pathway activity. Aldose reductase enzyme then catalyzes the formation of glucose to sorbitol in this pathway along with the oxidation of the NADPH to NADP+. Then by sorbitol dehydrogenase, sorbitol oxidized to fructose. Affinity of the AR enzyme for glucose gets higher during hyperglycemic states. Since sorbitol is not diffusible through cell membranes easily, it accumulates in tissues which are not insulin sensitive such as- retina, peripheral nerves and glomerulus. Which leads to generate intracellular osmotic stress or osmotic damage in that particular region. As a result of this condition neuropathic occurs and this disease condition gets severe over time. (Schreiber A , Nones C, Reis R, Chichorro J, 2015)

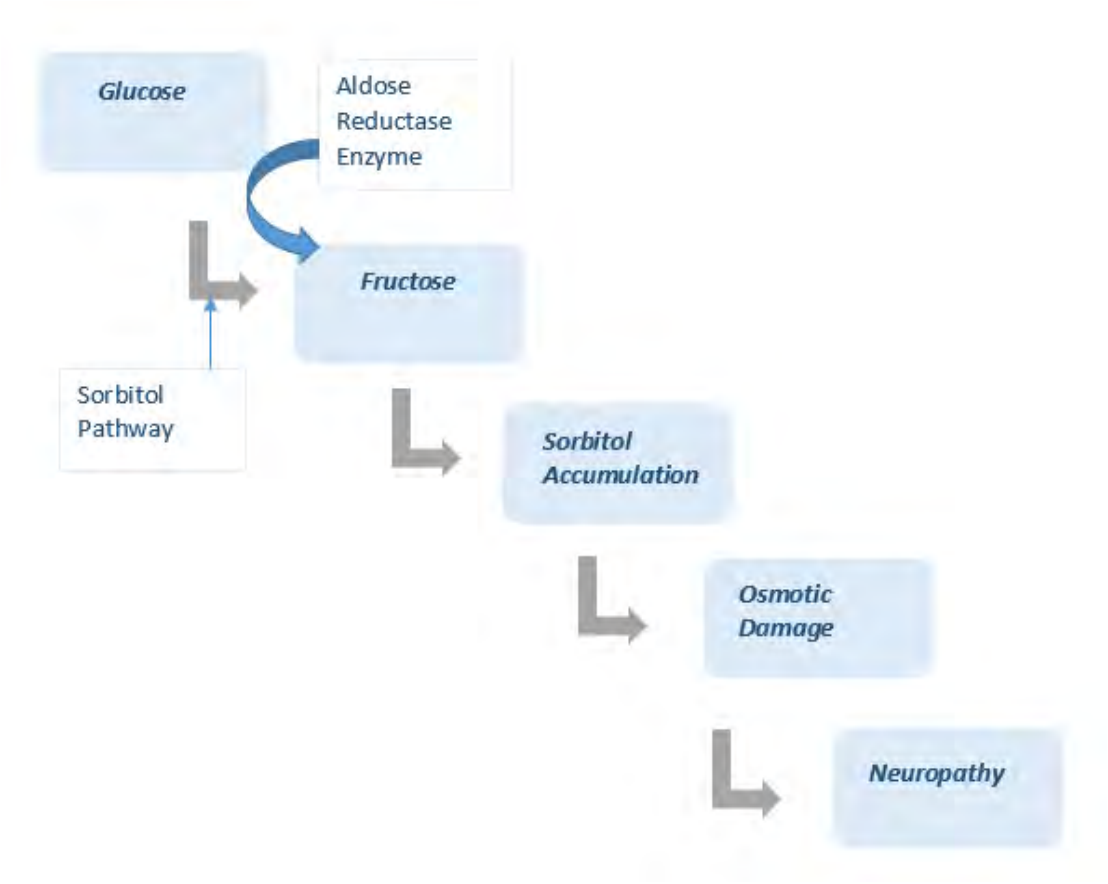

Figure 3.1.1: Mechanism of Action of Diabetic Neuropathy

3.1.2 Factors

Prevalence rate of Diabetic Neuropathy varies upon few factors. Their statistical analytical study data are given below-

Increasing Age- The prevalence rate of diabetic neuropathy varies according to this variable in a way that shows- from 11.1% in those 23 to 40 years old group to around 32.3% in the age range of 60 to 80 years' group. Thus is established that prevalence rate was increased with increasing age. (Morkrid, 2010) Duration of Diabetes- The more the duration the more the diabetic neuropathic complication occurs. It is estimated from a data- severity increase from 14.1% in patients with 5 years to around 29.2% in diabetic patients along with 9 to 11 years of age duration. (Morkrid, 2010)

3.1.3 Signs and Symptoms

Diabetic Neuropathy arrives with variety of complications and leads to dysfunctional behavior of certain body parts. The most common types of neuropathy are those who causes peripheral nerve dysfunction, shooting, tingling pain in nerves. In addition, this may also affect limbs and those may directly or indirectly affect organs and muscles inside the body. (S Inzucchi, J Rosenstock, 2012)

Distal Polyneuropathy affects the sensitivity of legs, hands, arms, feet. Can also affect the movement of limbs. Thus symptoms might be observed as-

a. Tingling, Burning sensation

b. Numbness or loss of sensation sometimes

c. Muscle Weakness or Discomfort

d. Skin Ulcers

e. Spontaneous pain

f. Muscle cramps

Almost half patients of such condition might not have certain symptoms, except for loss of sensation in feet. Because of such sensational loss they could injure their feet and might not know it. This untreated foot injury may lead to infections, ulcers and probably amputations.

Autonomic Neuropathy affects the digestive system, sweat glands, urinary tract, eyes, heart and sex organs. Symptoms may include-

a. Dizziness while standing up for a while

b. Digestive system issues (nausea, diarrhea, vomiting, bloating, constipation)

c. Too much or too little sweating

d. Bladder issues (frequent urinary tract infections, loss of bladder control)

e. Sexual problem in women and erectile dysfunction in men

Signs may include-

a. Lower motor neuron weakness

b. Reflexes

c. Vibration sense

3.1.4 Diagnosis

According to the American Academy of Neurology recommends that this diabetic neuropathy disease complication needs to be diagnosed in the presence of autonomic and somatic neuropathy when the other causes of neuropathy has been let off. Around 10% of patients suffering from diabetes may have neuropathic complication due to other causes. Diabetic neuropathy can asymptomatic in few patients thus it has to be diagnosed with careful examination. The required necessary criteria in this case would be- signs,

electrodiagnostic tests, symptoms, quantitative sensory test and autonomic test. (V Bansal, J Kalita, 2017) So beside physical exams, diagnosis of such complication are-

a. Neurological Examination- In such test health practitioner or doctor checks tendon reflexes of patient, the strength and of muscles, ability to feel particular sensations and coordination with posture.

b. Full Medical History- the doctor will review the whole medical background of the patient along with family history to mainly find out presence of any nervous system or neurological disease. Moreover, the symptoms, lifestyle, exposure to toxins and drinking habit should also be looked upon to.

c. Blood Tests- Blood tests will detect diabetes, vitamin deficiencies, any abnormality in immune functions along with other conditions which may cause diabetic neuropathy.

d. Imaging Tests- CT or computerized tomography, MRI scans or magnetic resonance imaging can be used for detection of any tumors, herniated disks or any other relevant abnormalities or indication.

e. Nerve Function Tests- Here an Electromyography is used which is to to record electrical activity in muscles for the detection of any nerve damage. There is probe which sends the electrical signals towards a nerve; then the electrode is placed along in the pathway of nerves which records the reaction of nerves to certain signals. This belongs to the study of nerve conduction.

f. Nerve Biopsy- Such a procedure refers to remove a small sensory nerve portion, to further check for idiosyncrasies.

g. Skin Biopsy- In this test, the health practitioner a small certain portion of skin in order to detect or look for any sort of reduction or abnormality in the nerve endings.

h. Other Nerve Function Tests- This includes autonomic reflex screen which detects or determines the functional activity of autonomic nerve fibers. Few sensory tests which checks for how the patient feel or react touch, vibration, heating and cooling affect along with a sweat test.

3.1.5 Management

Management of DPN efforts to adjust or modify the symptomatic situation or natural history to some acceptable extent. It was demonstrated that aggressive glycemic control where successful in reducing the risk and rate of progression of diabetic peripheral neuropathy. (Juster-Switlyk & Smith, 2016) Thus such type of modification aims at preventing or reducing the progression of neuropathic complications to some extent and serving symptomatic aid.

Glycemic Control-

It refers to a medical term indicating typical levels of blood sugar in patients who have diabetes mellitus. The relation between the development of neuropathic severity and hyperglycemia was estimated form a study. According to this study, 440 patients of diabetic condition were followed up, for long 25 years. This follow up indicated an increase in diabetic neuropathic complication which were clinically detectable; observable rise of prevalence of DN were 12% during the time of diagnosis of diabetic disease condition to about nearly 50% after 25 years of age; to add on those who had poor control in diabetic condition were found to have the highest prevalence.

In another study, prevalence rate of diabetes was reduced to 50% in those who were treated with intensive insulin during a period of long 5 years.

Lifestyle Changes-

Few small analytical studies show that, change or modification in lifestyle, including exercise, balanced diet might be beneficial to slow down the progress of diabetic neuropathy through stimulating the small nerve fiber regeneration in DN patients who have diabetic or pre-diabetic disease condition. Such measures would be-

a. Exercise- Regular exercise respective to one`s physical condition such as walking may decrease neuropathy complications like, pain, improvement in muscle strength and may also help to obtain an ideal blood glucose level respective to individuals' condition. Gentle routine of yoga may also prove to be beneficial.

b. Healthy Diet- Good nutritional supply is responsible for assuring the presence of essential vitamins and minerals. This might include vegetables, fruits, lean proteins and whole grains in regular diet.

c. Quit Smoking- Smoking can affect the body`s circulation leading to an increased risk foot problems and other neuropathic complications. Thus it's wiser to quit such consumption before considering any treatment for diabetic neuropathy.

d. Foot Care, especially in Diabetic condition- A regular check should be conducted for cuts, blisters. Wearing soft, padded shoes and loose or unfastened cotton socks can be beneficial.

e. Avoid Excessive Alcohol Consumption- As habit or addiction excessive alcohol can worsen diabetic neuropathic complications.

f. Regular Monitoring of Blood Sugar Level- In order to keep the blood glucose level under control regular monitoring is necessary. This might also help to improve neuropathic condition. Because neuropathic complication gradually lessens in accordance to euglycemic balance.

3.1.6 Treatment

Medications

a. Antidepressants- They are prescribed because such medicines are found to relieve pain by the interference in the chemical process of brain and spinal cord , that instructs the nerves of our body to sense pain. Such as- Amitriptyline, Imipramine, Nortriptyline.

b. Anti-epileptics- This class of medicine is well accepted for the treatment of painful nerve condition since it may relieve nerve associated pain. Such as- Topiramate, Gabapentin, Pregabalin.

c. Pain Reliever- NSAIDs and over the counter drugs to relieve mild painful symptoms. In more severe case doctor may suggest Painkillers in a balanced schedule respective to individuals' health.

d. Topical Treatment- Creams may be used for topical treatment. Such creams may cause burning or irritation in the skin area where it is applied, but gets lessen over time. Such as- Capsaicin cream. (Huizinga & Peltier, 2007)

Class of Medicine	*Name of the Drugs*	*Recommended dose*	*Adverse Events*
Antidepressants	a. Amitriptyline	100-150 mg per day (75 mg twice per day or 150 mg at bedtime)	Confusion, dry mouth, sedation, dizziness, blurred vision, arrhythmias, weight gain, urinary retention, constipation.
	b. Imipramine	150 mg/day (75 mg twice daily)	Sedation, confusion, dizziness, dry mouth, orthostatic hypotension, urinary retention, weight gain, blurred vision, constipation.
Anti-Seizure or Anti-Epileptics	a. Gabapentin	2400-3600 mg/day (900 mg four times per day or 1200 mg thrice per day)	Dizziness, nausea, somnolence, ataxia, constipation, leucopenia, dry mouth, weight gain, nystagmus.
	b. Pregabalin	300-600 mg/day (200 mg thrice per day or 300 mg two times per day)	Dizziness, ataxia, blurred vision, weight gain, peripheral edema, tremor, somnolence, diplopia. **Rare:** acute renal failure, thrombocytopenia, rhabdomyolysis.
Topical Treatment	Capsaicin cream	As prescribed by the physician.	Cough, localized burning, sneezing, itching.
Combination Medicine	Epalrestat+ Methylcobalamin+ Pregabalin	150mg+ 1500 mcg + 150mg	Dizziness, weakness, confusion, skin rash, sweating, fast heart rate, irritability.

Table 1.2: Classes of Medicine with their Different Aspects

3.1.7 Therapies

a. Transcutaneous Electrical Nerve Stimulation- Here an electrode is positioned appropriately on skin, in order to deliver a gentle electrical current at certain varying frequencies. Such therapy is taken 30 minutes daily for a month.

b. Physical Therapy- In case of muscle weakness, physical therapy may improve the situation to some extent.

c. Surgery- If neuropathy is caused by any sort of pressure in the nerves for example- existence of tumors, surgical treatment might reduce the pressure.

This overall review shows that such medicinal treatment for DN causes several symptomatic complications. Along with all other treatment option a new addition to this context is a reversible Aldose Reductase Enzyme Inhibitor. Which is known as EPALRESTAT.

It inhibits the neuropathic complication with minimum side effects. Thus as considering it as a better treatment option, our projects intends to develop a sustained release dosage of it for prolonged therapeutic effect.

3.2 Epalrestat

Epalrestat is a carboxylic acid derivative and a non-competitive drug which reduces the aldose reductase enzyme and thus inhibits the accumulation of intracellular sorbitol in peripheral nerves.

The IUPAC name of Epalrestat is known as-

2-[(5Z)-5-[(E)-2-methyl-3-phenylprop-2-enylidene]-4-oxo-2-sulfanylidene-1,3-thiazolidine-3-ly] acetic acid

Chemical Formula- $C_{15}H_{13}NO_3S_2$

Molar Mass- 319.401 gm/mol

Density- 1.43gm/cm3

Melting Point- 210 ℃ (410 ℉; 483K)

Boiling Point- 516.8℃ (962.2℉; 789.9K)

All the data were obtained in room temperature which is 25℃.

The brand names of Epalrestat in different countries are-

Aldonil, Alrista, Eparel 50, Eplistat 150 SR, Listap-50 (India)

Aldorin (Bangladesh)

Tanglin (China)

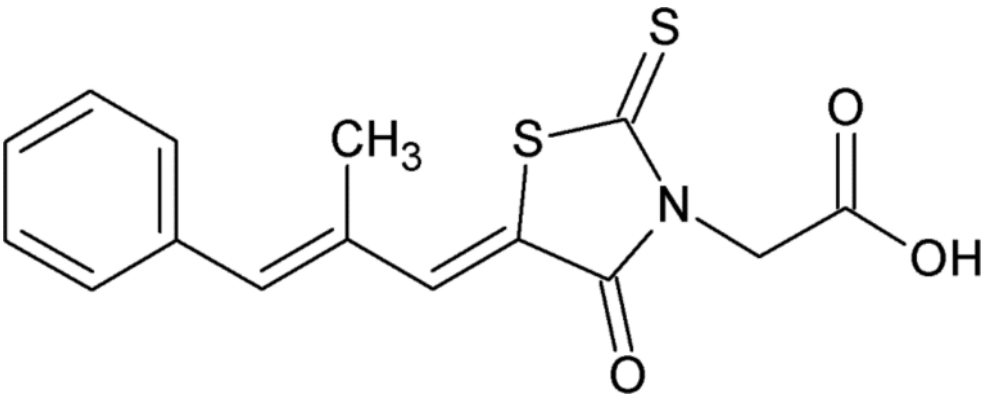

Figure 3.2: Chemical Structure of Epalrestat

3.2.1 Mechanism of Epalrestat

The enzyme AR which catalyzes the sorbitol pathway and thus leads to sorbitol accumulation in peripheral nerves, is reduced or inhibited by Epalrestat drug.as a result sorbitol accumulation also gets inhibited. Thus it suppresses the osmotic damage and ultimately cures neuropathic complication or pain.

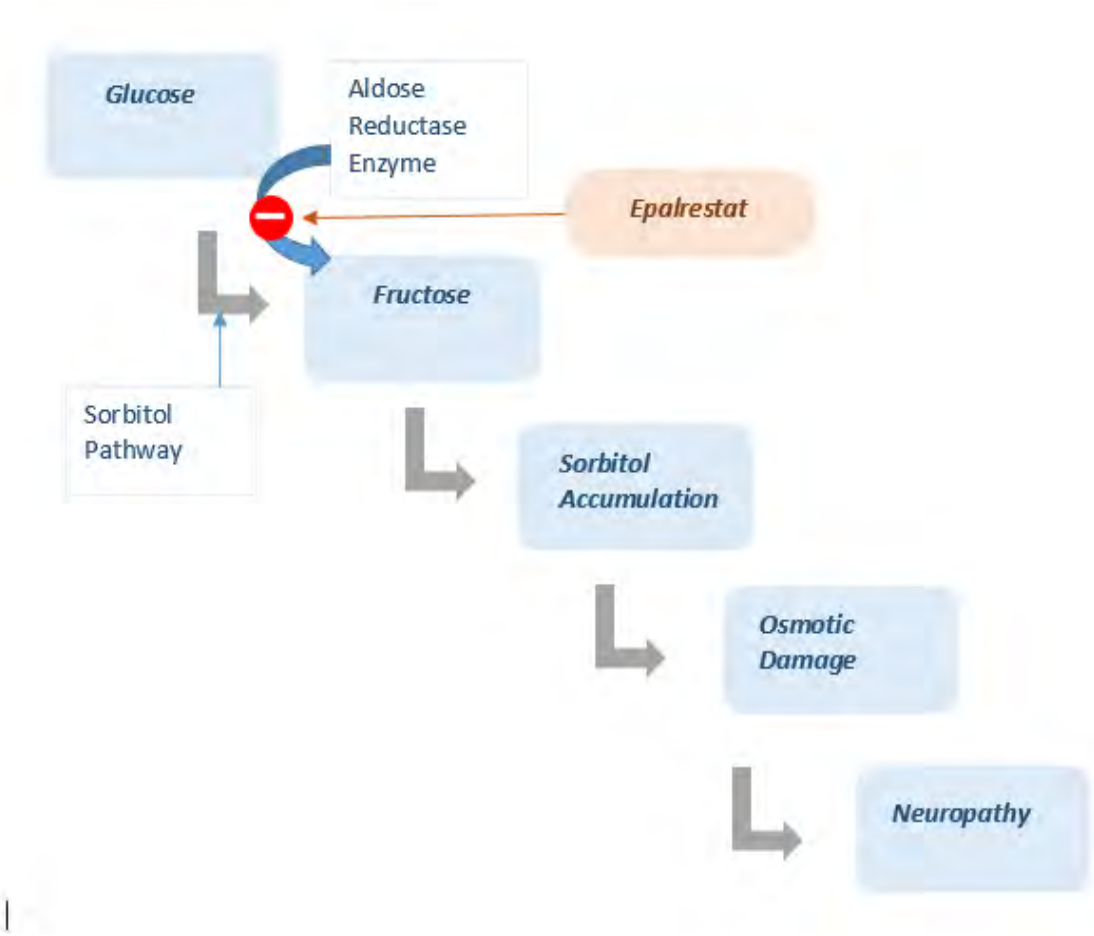

Figure 3.2.1: Mechanism of Action of Epalrestat Drug in Treatment of DN.

3.3 Preferable Choice

Epalrestat is a preferable medication choice in the treatment of diabetic neuropathy for various efficient reasons. Such as-

a. Easily absorbed in the neural tissues to generate therapeutic effect.

b. Inhibits the AR enzyme with minimum side effects. For example- rash, chills, nausea, vomiting, GI issues, weakness or discomfort, dizziness, abdominal pain in short all the general symptoms which is not very harmful and bearable.

c. Does not influence Glycemic control while acting in the circulation.

d. No significant change in hematological and biochemical parameters.

According to a statistical analysis, 6.7% of patients reported side effects who were treated with Epalrestat, whereas 11.5% patients reported side effects who took Methylcobalamin for DN.

3.4 Dosing Schedule

Usually prescribed to be taken orally thrice per day for immediate therapeutic action in case of IR dosage form.

4. Conclusion

The review stands for the analysis of Diabetic Neuropathy related terms in association with relevant statistics of such complication in the context of Bangladesh. The field of treatment involves few medications along with different therapies each having more or less adverse drug reactions. Amongst all medication option, a preferable choice was found in Epalrestat, an aldose reductase enzyme inhibitor drug.

Epalrestat signifies its preference over other drugs through some excellent pharmacokinetic and pharmacodynamic features. However, the aim of this project work is to modify its usual dosing schedule for better therapeutic purpose.

Thus, this project intends to develop a sustained release dosage form of this existing drug with proper evaluation and assessment. Because a sustained or modified release dosage form will offer a prolonged duration of drug release and eventually longer duration of action. Thus, a prolonged therapeutic effect will be obtained. This may also help to minimize the severity of certain side effects.

So far, in the experimental lab work, a standard curve of Epalrestat with certain concentration was prepared. After several trials exactly on the ninth trial, a standard method for this tablet manufacture was optimized. Following this method further designing and tablet forming will be performed. This future work includes preparing tablets with five different formulas each having different quantities of ingredients. Then evaluation will be performed with different parameters to assess the effectiveness of the developed or modified form of Epalrestat.

By this project on Epalrestat, we hope to serve a positive and beneficial result in the field of Diabetic Neuropathy Treatment in our country.

5. References

Abdulfatai B. Olokoba, Olusegun A. Obateru, L. B. O. (2012). Type 2 Diabetes Mellitus: A Review of Current Trends. *Oman Medical Journal*, *27*(6022). https://doi.org/10.1136/bmj.1.6022.1371

Akter, S., Rahman, M. M., Abe, S. K., & Sultana, P. (2014). Prevalence of diabetes and prediabetes and their risk factors among Bangladeshi adults: a nationwide survey. *Bulletin of the World Health Organization*, *92*(3), 204–213A. https://doi.org/10.2471/BLT.13.128371

Deli, G., Bosnyak, E., Pusch, G., Komoly, S., & Feher, G. (2013). Diabetic neuropathies: Diagnosis and management. *Neuroendocrinology*, *98*(4), 267–280. https://doi.org/10.1159/000358728

Harikumar, K., Kumar, B. K., Hemalatha, G. J., Kumar, M. B., Fransis, S., & Lado, S. (2014). REVIEW ARTICLE A Review on Diabetes Mellitus. *INTERNATIONAL JOURNAL OF NOVEL TRENDS IN PHARMACEUTICAL SCIENCES A*, *4*, 201–217.

Huizinga, M. M., & Peltier, A. (2007). Painful Diabetic Neuropathy : A Management-Centered Review, *25*(1), 6–15.

Juster-Switlyk, K., & Smith, A. G. (2016). Updates in diabetic peripheral neuropathy. *F1000Research*, *5*(0), 738. https://doi.org/10.12688/f1000research.7898.1

Morkrid, K. (2010). "The prevalence of and risk factors for diabetic peripheral neuropathy among type 2 diabetic outpatients in Bangladesh." *International Journal of Diabetes in Developing Countries*, *30*(1), 11–17. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2859278/

Rao, S., & Vv, J. (n.d.). Review article type 2 diabetes mellitus - exploring the avenue of bariatric surgery.

Rolim, L. C., da Silva, E. M. K., De Sá, J. R., & Dib, S. A. (2017). A systematic review of treatment of painful diabetic neuropathy by pain phenotype versus treatment

based on medical comorbidities. *Frontiers in Neurology*, *8*(JUN). https://doi.org/10.3389/fneur.2017.00285

Rowe, R. C., Sheskey, P. J., & Owen, S. C. (n.d.). *Handbook of Pharmaceutical Excipients*. London.

S Inzucchi, J Rosenstock, G. U. (2012). Diabetic neuropathy. *Annals of Neurology*, *15*(1), 2–12. https://doi.org/10.1002/ana.410150103

Schreiber A , Nones C, Reis R, Chichorro J, C. J. (2015). Diabetic neuropathic pain: Physiopathology and treatment. *World Journal of Diabetes*, *6*(3), 432. https://doi.org/10.4239/wjd.v6.i3.432

Shende, S. D., Baig, M. S., & Doifode, S. M. (2018). Evaluation of Efficacy and Safety of Epalrestat (150 mg) Compared to Epalrestat (50 mg) in Patients Suffering from Diabetic Peripheral Neuropathy. *Journal of Clinical and Diagnostic Research*, *12*(4), 15–19. https://doi.org/10.7860/JCDR/2018/32716.11444

V Bansal, J Kalita, U. K. M. (2017). Diabetic neuropathy. *Diabetes and Aging-Related Complications*, 31–43. https://doi.org/10.1007/978-981-10-4376-5_3