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DESIGN, DEVELOPMENT AND EVALUATION OF BI-LAYERED TABLET OF PREGABALIN

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Abstract

Tablets containing Hydralazine HCl and Pregabalin by Direct compression technology was to formulate a stable, safe and convenience dosage form for the better management of most common cardiovascular disorders or blood pressure. The formulations of bilayer tablets showed good results in case of Hydralazine HCl immediate release layer physicochemical parameters and prepared using concentration of superdisintegrant sodium starch glycolate and ac-di-sol® for the fast release layer and sustained release layer of pregabalin containing HPMC K100 M and polyox^{tm} WSR 303 for the delay the drug release up to 10-12 hrs. The FTIR and DSC analysis indicates that there were no drug-drug and drug-excipients interactions. Pre compression and post compression parameters were found to be within the satisfactory limits and hence suitable to formulate Bilayer tablets. Formulation batch HDID was finally optimize in which HD9 (Hydralazine HCl) batchis selected as immediate release layer and ID9 (pregabalin) batch is selected as sustained release layer as final selected formulation. Batch HDID provides better drug release profile. The data obtained from *in vitro* release study were fitted to various mathematical models like Higuchi and Peppas model exponential coefficient 'n' < 0.5 indicates that the release was governed by Fickian diffusion..

Keyword: Hydralazine HCl, In vitro release, Preformulation and Pregabalin

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1. Introduction :

Hypertension, elevated blood pressure, is a noteworthy public health concern worldwide due to its significant contribution to the global health burden and its role as a prominent risk factor for the development of a number of disease processes. In the year 2019, high blood pressure accounted for 54% of stroke, 47% of ischemic heart disease, 75% of hypertensive disease, and 25% of other cardiovascular disease worldwide. The negative impact of hypertension on health status is clear, especially taking into account the disability, decreased quality of life, and mortality associated with stroke and cardiovascular disease. In 2019, 7.6 million deaths (13.5% of all deaths) and 92 million disability life-years (6% of total) were attributable to systolic blood pressure greater than 115 mmHg . It is saddening to note that such pervasive negative effects are related to such a modifiable cause.[1]

Oral route has been the major route of drug delivery for the chronic treatment of many diseases. The purpose of the present work was to develop an optimized bilayer tablet for anti-hypertension patients using hypertensive agent as a model drug candidate by optimization technique. Combination drug therapy is recommended for treatment of hypertension to allow medications of different mechanism of action to complement each other and together effectively lower blood pressure at lower than maximum doses of each.

The goal of any drug delivery systems is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. Two aspects are most important to drug delivery, namely spatial placement and temporal delivery of a drug[4]. Spatial placement related to targeting drug to a specific organ or tissue. While temporal delivery refers to controlling the rate of drug delivery to the target tissue. The objective of this study was to develop an optimized GFDDS containing sustained release & immediate release model drug—a peroral intragastric floating dosage form having a bulk density lower than that of gastric fluids and remaining buoyant on the stomach contents.

To achieve the objectives, independent formulation variables like total polymer content-to-drug

ratio, polymer-to-polymer ratio, and different viscosity grades of polymers will be use.

2. Material and Methods

Preparation of 0.1N HCl

0.1N HCl was prepared by diluting 8.5 ml of concentrated Hydrochloric acid to 1000 ml distilled water. Final pH of above solution was then measured with pH meter and adjusted to pH 1.2.

HPLC Assay Method for Determination of Drug

Standard preparation

Take about 10 mg of Standard Pregablin(25% Diluted) and about 10 mg Standard of Hydralazine HCl transfer into a clean and dry 25 ml volumetric flask, addabout 15 ml of mobile phase mix to dissolve it and make up 25 ml volume with mobilephase and mix.

Test preparation

Take about 10 mg of Standard Pregablin(25% Diluted) and about 10 mg Standard of Hydralazine HCl transfer into a clean and dry 25 ml volumetric flask, addabout 15 ml of mobile phase mix to dissolve it and make up25 ml volume with mobilephase and mix.

Preparation of Standard Calibration Curve of Hydralazine HCl

The construction of standard calibration curve of Hydralazine HCl was prepared by using mix volume of methanol and distilled water 1000ml containing 0.1ml TEA each(60:40). From the stock solution, take 50, 75, 100, 125, 150 µg/ml solutions were prepared respectively. Take the absorbance of above samples at $\lambda_{max.}$ 215 nm. The standard graph of Hydralazine HCl was constructed by taking the peak area on Y-axis and concentrations on X-axis.

Preparation of Standard Calibration Curve of Pregablin

The construction of standard calibration curve of Pregablin was prepared by using mix volume of methanol and distilled water 1000ml containing 0.1ml TEA each(60:40). From the stock solution, take 50, 75, 100, 125, 150 µg/ml solutions were prepared respectively. Take the absorbance of above samples at $\lambda_{max.}$ 215nm. The standard graph of Pregablinwas constructed by taking the peak area on Y- axis and concentrations on X-axis.

Pre-formulation Study

Pre-formulation studies are the first step in the rational development of dosage form of a drug substance. The objective of pre-formulation studies is to develop a portfolio of information about the drug substance, so that this information useful to develop different dosage form. Pre-formulation can be defined as investigation of physical and chemical properties of drug substances alone and when combined with excipients.

Identification of Drugs

Identification of Hydralazine HCl and Pregablin by FT-IR Infrared (IR) spectroscopy was conducted using a FT-IR Spectrophotometer (Shimadzu 8400S) and the spectrum was recorded in the wavelength region of 4000 to 600 cm^{-1}.The procedure consisted of dispersing a drug in KBr and compressed into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed inthe light path and the spectrum was obtained.

Identification of Hydralazine HCl and Pregablin by DSC

The DSC study was carried out using DSC-60 (Shimadzu, Tokyo, Japan). The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. The drug was heated in sealed aluminum pans under nitrogen flow (30ml/min) at a scanning rate of 5^0C/min from 50 to 300^0C. Empty aluminum pan wasused as a reference. The heat flow as a function of temperature was measured for the drug.

Table 6.2: Area of different concentration of Pregabalin

Concentration (µg/mL)	Peak Area
0	0
50	6254635
75	9629461
100	12700701
125	15965898
150	18934406

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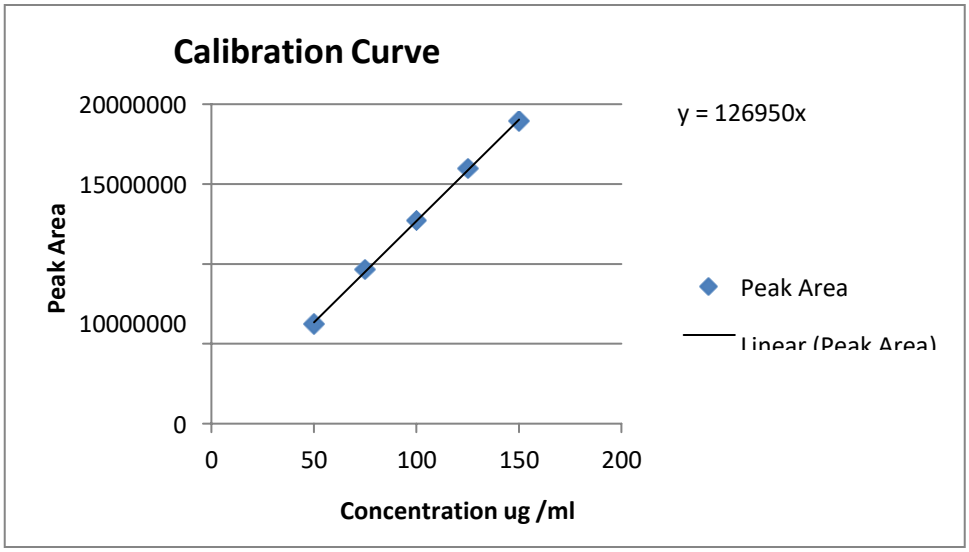

Figure 6.5: Calibration Curve of Pregabalin

Identification of Drugs

Identification of Hydralazine HCl by FT-IR

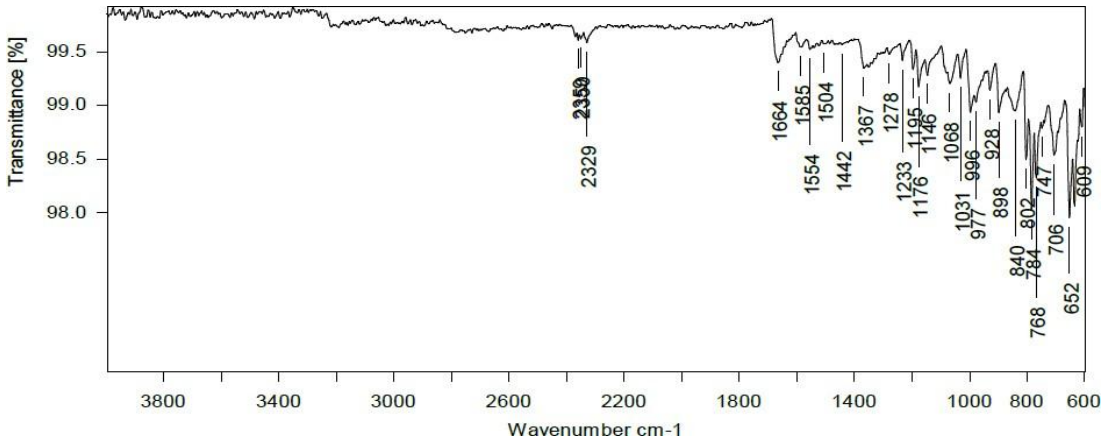

Figure 6.6: FT-IR Spectra of Hydralazine HCl SUMMARY

Hypertension affects around half of the adult population worldwide, being one of the most common cardiovascular disorders (CVD). It occurs when the high cardiac outputexerts pressure on the arterial wall as the blood flow increases. The conventional dosage form used in the treatment of hypertension cannot produce the desired therapeutic effect for a prolonged period. The rationale for using fixed-dose combination therapy is to obtain increased blood pressure

(BP) control by employing two antihypertensive drugs with different modes of action and enhance compliance byusing a single tablet. Bilayer tablet is suitable for the sequential release of two drugsin combination, separate, and sustained release.

Bilayer tablets are able to provide multiple releases kinetic of same/different drug. It is preferred to co-administer two different drugs in the same dosage form and controlling drug release rate of two different API. It is also preferred to reduce of pill burden and safety margin of high potency drug can be increased.

The rational for combination therapy is to encourage the use of lower doses of drug to reduce the patient's blood pressure to goal to minimize dose dependent side effects and adverse reactions. When smaller doses of medication with different mechanism of action are combined, synergistic or additive effects on blood pressure are achieved and dose dependent side effects are minimized. Here in the present study two drugs Hydralazine HCl and Pregabalin are used in the combination.

Hydralazine HCl, a directly acting as potent peripheral vasodilator, is widely prescribed in the treatment of hypertension and congestive heart failure by direct relaxation of arteriolar smooth muscle. While, Pregabalinis relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end diastolic pressure and pulmonary capillary wedge pressure. The combination consists of Hydralazine HCl 25 mg and Pregabalin40 mg fixed-dose that functions as a nitric oxide enhancer and an antioxidant that helps to prevent tolerance to the prolonged use of nitrate. This combination also balanced after-load and pre-load reduction with a lowering of ventricular filling pressure and systemic and pulmonic vascular resistance. The hemodynamic effects of the combination drug in heart failureinclude increased cardiac output.

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