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Formulation and *In- Vitro* evaluation of tolperisone hcl buoyant tablet

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ABSTRACT

The aim of present investigation was undertaken with the objective of formulating buoyant tablet of Tolperisone HCl. Tolperisone HCl is a skeletal muscle relaxant. Drug is more stable in acidic medium (pH < 4.5), and in alkaline medium (pH 4 to 7) tolperisone breaks down into 4-MMPPO [2methyl-1-(4methylphenyl)-propanone] and piperidine. Thus, the patient is exposed to an uncontrollable quantity of genotoxic agent 4-MMPPO. 3^2 full factorial designs were used for optimization of formulation variable. The drug: polymer ratio (X1) and concentration of sodium bicarbonate (X2) were selected as independent variables, while time required for drug release 50% (t50), time required for drug release 90% (t90), drug release at 12hr (Q12), Floating lag time, release rate constant (k) and diffusion exponent (n) were selected as a dependent variable. Prepared tablets were evaluated for pre compression and post compression parameters. The release mechanisms were explored and explained by applying zero order, first order, and Higuchi and Korsmeyer equations. Regression analysis and analysis of variance were performed for dependent variables. Optimized formulation (B6) showed 99.27% drug release at the end of 24 hrs and maximum similarity factor (f2= 74.41) and minimum dissimilarity factor (f1= 4.24) with theoretical release profile of Tolperisone HCl. Optimized formulation followed by anomalous nonFickian release mechanism and found to be stable after 21 days at accelerated condition.

Keywords: Antifungal activity, Gelling agent, Hydrophobic drugs, Micro emulsion gel, Topical drug delivery.

INTRODUCTION

The gastro retentive drug delivery system can be retained in the stomach and assist in improving the oral control delivery of drug that have an absorption window in a particular region of the gastrointestinal tract. This system helps in continuously releasing the drug, thus ensuring optimal bioavailability. The matrix tablet composed of drug and the release retarding material offers the simplest approach in designing of control release system. Skeletal muscle relaxants are drug that acts peripherally at neuromuscular junction or muscle fibre itself or centrally in the cerebrospinal axis to reduce the muscle tone. Centrally acting muscle relaxants are used mainly for painful muscle spasm and spastic neurological condition. Tolperisone HCl causes muscle relaxation by its action on central nervous system. It also leads to membrane stabilizer and has analgesic activity. It has also been usedin treatment of condition which in cludes dysmenorrhoea, climacteric complaints, lockjaw, and neurolatyrism.

Tolperisone HCl is a "Class-I" drug according to Bio-pharmaceutics Classification System, possessing both high solubility and high permeability absorption characteristics. Tolperisone HCl is rapidly and completely absorbed from the gastrointestina l tract. Peak plasma concentrations are reached0.9-1.0 hours afteroral dosing. Tolperisone HCl breaks down into 4-MMPPO [2 Methyl-1-(4- methyl phenyl)-propanone] and piperidine hydrochloride when undergoes into intestinal pH at 4 to 7. Thus the patient is exposed to an uncontrollable quantity of 4- MMPPO which causes genotoxicity. This problem is overcome by controlled release of tolperisone hydrochloride in the stomach at pH 1 to 2. Tolperisone HCl has a short biological half life (1.5 - 2.5hr). If it is formulated as conventional tablet it will require 150mg -450mg (2-3 times daily) in divided dosage. So it makes the tolperisone hydrochloride an ideal candidate for the control drug delivery [1].

MATERIALS

Tolperisone.Xanthan, Gum, Guar Gum and Dibasic calcium phosphate (DCP).Sodium bicarbonate, Magnesium stearate, Talc.

METHOD

Preparation of Tolperisone HCl Buoyant Tablets
Method: Direct Compression

Direct compression was followed to manufacture the gas generating buoyant tablets of Tolperisone HCl. All the ingredients were accurately weighed **a n d** pass through sieve no. 60 before using into formulation. Compressed on 10 station rotary tablet machine using caplet punch. The tablets were compressed to obtain hardness in a range of 6-7 Kg/cm^2.

Evaluation of Powder Blend and Tablets Drug-Excipients Compatibility study

Fourier transform infrared spectroscopy has been used to study the physical and chemical interaction between drug and the excipients used. Fourier transform infrared (FTIR) spectra of Tolperisone hydrochloride, Xanthan Gum were recorded using KBr mixing method [2].

Loose Bulk Density

Weigh accurately 5 gm of powder blend, and transferred in 100 ml graduated cylinder. Carefully level the powder blend without tcompacting, and read the unsettled apparent volume (V_0). Calculate the apparent bulk density in gm/ml by the following formula: Bulk Density = Mass/ apparent volume

Tapped Bulk Density

Weigh accurately 5 gm of powder blend, and transferred in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V_1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume (V_2) to the nearest graduated units, if the difference between the two volumes is less than 2% then final the volume (V_2). Calculate the tapped bulk density in gm/ml by the following formula:

Tapped Density = Mass/ tapped volume

Carr's Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the Bulk Density and Tapped Density of a powder blend and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's Index = Tapped Density-Bulk Density×100/ Tapped Density

Hausner's Ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder blend material. Hausner's Ratio = Tapped Density/Bulk Density

Angle of Repose

The angle of repose of powder blend powder was determined by the funnel method. The diameter of the powder blend cone was measured and angle of repose was calculated using the following Equ. Angle of Respoce

$(\square)$ = tan-1h/r

Where, h =Height of the powder blend cone r =Radius of the powder blend cone [3].

Weight Variation Test

The 20 tablets were selected at random, weighed and the average weight was calculated. Not more than two of the individual weights should deviate from the average weight by more than 10%.

Friability

For each formulation, pre weighed tablet sample (10 tablets) were placed in the Roche friabilator which is then operated for 100 revolutions. The tablets were deducted and re-weighed. Conventional compressed tablets that loose <0.5 to 1% of their weight are considered acceptable [4].

Hardness

Hardness of tablet was determined using Monsanto hardness tester.

Content Uniformity The20tabletswerecrushedandthepowderequivalentof100mg of drug was transferred to100ml of 0.1N HC1 in volumetric flask. The solution was analyzed at 261 nm using double beam UV-Vis spectrophotometer after suitable dilution. The content of drug was calculated from calibration curve.

In-vitro buoyancy study

The In-vitro buoyancy was characterized by floating lag time (FLT) and total floating time (TFT). The test was performed using USP24 type II paddle apparatus using 900 ml of 0.1 N HC1 at 50 rpm at $37\pm0.5°C$. The time required for tablet to rise to surface of dissolution medium and duration of time the tablet constantly float on dissolution medium were noted as FLT and TFT, respectively [5].

In vitro drug release study

The In vitro drug release was performed using USP-24 type II paddle apparatus in 900 ml of 0.1N HC1 at 50 rpm at $37 \pm 0.5°C$. The samples were withdrawn at pre- determined time intervals for period of 24 hr and replaced with the fresh medium. The samples were filtered through 0.45µm membrane filter suitably diluted and analyzed at 261 nm using double beam UV- Vis spectrophotometer. The content of drug was calculated using calibration curve.

Kinetic model for release data

The drug released data of all batches were fitted with desired kinetic model such as Zero order kinetic, First order kinetic, Higuchi model and Korse meyer peppas model to ascertain the drug release. The Zero order and First order drug release. The Zero order and First order drug release explain the drug release depend on drug concentration or not. The Korse meyer peppas model described the

method of The Drug release and Higuchi model described the diffusional drug release.

Zero order = $Q_1 = Q_0 + K_0 t$

First order = $Q_t = Q_0 e^{-K_1 t}$

Higuchi model = $m = (100-q) \times t^{1/2}$

Hixon Crowell Model = $W_0^{1/3} – W^{1/3} = kt$ Korsemeyer peppas model = $Mt/M\alpha = K \times t^n$

Where Q_1 is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution, Q_t is the amount of drug dissolved in time t, W_0 is initial amount of drug in dosage form, W_t is remaining amount of drug in dosage form at time t, Mt/Mα is the fraction of drug release at time t and n is diffusion exponent. K_0, K_1, and k refer to the rate constant [6, 7].

Statistical analysis

The statistical analysis of the factorial design batches was performed by multiple regression analysis using Microsoft Excel. Polynomial models were generated for all the response variables using Microsoft Excel. In addition analysis of variance (ANOVA) was used to identify significant effects of factors on response regression coefficients. The F value and p values were also calculated using Microsoft Excel. The relationship between the dependent and independent variables was further elucidated using response surface plots [8, 9].

Similarity factor (f_2)

To evaluate and comparison of dissolution profiles, the dissolution profiles were analyzed using similarity factor f_2. The f_2 value between 50 and 100 suggests that the dissolution profiles are similar. The f_2 value of 100 suggests that the dissolution profiles are similar. The f_2 value of 100 suggests that the test and reference profiles are identical and as the value becomes smaller, the dissimilarity between releases profile increases.

Dissimilarity factor (f_1)

The dissimilarity factor (f_1) calculates the percent difference between the two curves at each time point and is a measurement of the relative error between the two curves. The values should lie between 0-15. For curves to be considered similar f_1 values should be close to 0.

Accelerated stability study

A variety of environmental factor such as temperature, humidity, and light, and to establish a re-test for the drug substance or a shelf life for the drug product and recommended storage condition. The storage condition used for stability studies were accelerated condition ($40^0 C \pm 2^0 C$ / 75 % $\pm$ 5% RH). Stability study was carried out for the optimized formulations. Tablets of optimized formulation were striped packed and kept in humidity chamber on above mention temperature [10,11, 12].

RESULT AND DISCUSSION

The drug and polymer were compatible with each other. The powder mixture used for tablet preparation were evaluated for pre-

compression parameter like bulk density, tapped density, Hausner's ratio, Carr's index, and angle of repose, are shown in. Tolperisone HCl floating tablets were prepared and evaluated for hardness, friability and drug content uniformity. From the dissolution profile it was observed that there was significant outcome of different polymers and polymer load on drug release. All batches exhibit initial burst release of drug due to rapid dissolution of drug from tablet surface. The kinetics of the dissolution data were well fitted to zero order, Higuchi model and Korsmeyer-Peppas model as evident from regression coefficients. The values of Dissimilarity factor (f_1) for batches B1, B2, B3, and B6 were less than 15 compared with theoretical dissolution profile indicating good similarity in dissolution. The batch B6 showed minimum value of f_1 (4.24). The values of similarity factor (f_2) for batches B1, B2, B3, and B6 were greater than 50 compared with theoretical dissolution profile indicating good similarity in dissolution. The batch B6 showed maximum value of f_2.

CONCLUSION

The present investigation was aimed to formulate and evaluate floating tablet of Tolperisone HCl were prepared by direct compression method based on natural polymers (e.g. Xanthan Gum and Guar Gum) as matrix forming material and different concentration of sodium bicarbonate as gas generating agents. FTIR spectroscopy indicates that the drug is compatible with the polymer. The concentration of Xanthan Gum and sodium bicarbonate were successfully optimized by using 3^2 factorial design. From the 3^2 factorial design and different graphical representation, it was finalized that batch B6 was found to be optimized batch having drug release up to 24 hr. More ever, the dissolution profile of optimized batch B6 was found to be similar with theoretical drug release profile having similarity factor more than 50 (f_2=74.41) and dissimilarity factor less than 15 (f_1=4.24) which reflects the feasibility of the optimization procedure in successful development of floating matrix tablet containing Tolperisone HCl by using Xanthan Gum. Various kinetic models of optimized formulation (B6) was best fitted into zero order model and Higuchi with anomalous non Fickian release mechanism. The optimized batch was found to be stable after 21 days at accelerated condition [13].

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