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EXTENDED-RELEASE TABLETS OF LOSARTAN POTASSIUM WITH XANTHAN GUM AND GUAR GUM AS RELEASE MODIFIERS

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ABSTRACT

A common hypertension medication, losartan potassium, is the subject of this investigation, which focuses on the formulation of extended-release tablets containing the medication. According to this inquiry, the release modifiers that were used were xanthan gum and guar gum. Both of these substances are well-known for their capacity to regulate the kinetics of drug release. The extended-release tablet forms of losartan potassium are primarily necessary for the long-acting impact at decreased dose frequency. Losartan potassium is one of the antihypertensive medications that is given to a large number of people and is taken orally. Exploring natural gums, namely xanthan gum and guar gum, as potential drug release modifiers was the primary objective of the current study, which attempted to create and optimize an extended-release tablet containing losartan potassium. A tablet formulation was produced, which was shown to contain all physical qualities within the intended range. Additionally, it demonstrated a sustained release profile, with about 70% of the medication being released over a period of 9 hours.

Keywords: -Xanthan gum, Kinetics, Therapeutic, Dosage, Drug.

I. INTRODUCTION

Extended-release tablets are an essential component in the formulation of pharmaceuticals because they provide a regulated and sustained release of active pharmaceutical ingredients (APIs) over a prolonged period of time. Over the course of the last several years, researchers and pharmaceutical experts have investigated a variety of formulation methodologies with the aim of improving the effectiveness of such dosage forms and increasing patient compliance. Extended-release tablets are an example of a noteworthy undertaking that incorporates the utilization of release modifiers such as xanthan gum and guar gum in the production of the tablets. For the purpose of shedding light on the formulation intricacies, release kinetics, and potential therapeutic benefits of this innovative drug delivery system, this introduction delves into the complexities of extended-release tablets that contain losartan potassium, an antihypertensive agent that is widely prescribed. Additionally, this introduction investigates the role of xanthan gum and guar gum as release modifiers. Due to the fact that it is both effective and well tolerated, the angiotensin II receptor blocker known as losartan potassium has acquired universal recognition in the healthcare industry for the treatment of hypertension. On the other hand, typical formulations of immediate-release medications sometimes need repeated daily doses, which may result in variations in the plasma levels of the drug as well as possible adverse effects. By delivering a therapeutic impact that is maintained and prolonged, lowering the frequency of administration, and increasing patient compliance, extended-release formulations provide a viable solution to this problem. These formulations have regulated release kinetics, which allows them to provide both of these benefits. Excipients and release modifiers must be carefully balanced in order to obtain the correct drug release profile when extended-release tablets are being formulated. This is a complicated procedure that requires careful attention to detail. In this particular situation, xanthan gum and guar gum, both of which are polysaccharides that exist naturally, have emerged as interesting

options. Because of their one-of-a-kind rheological qualities and mucoadhesive features, these hydrocolloids are well-suited for the purpose of regulating the release of drugs in pharmaceutical formulations. Because of their capacity to create a gel-like matrix when they are moistened, they contribute to sustained drug release, which results in a therapeutic effect that is both consistent and long-lasting. The bacteria Xanthomonas campestris is responsible for the fermentation process that results in the production of xanthan gum, which is an anionic polysaccharide of highly molecular weight. Because of its viscoelastic characteristics, water retention capacity, and pseudo plastic behavior, it is an excellent choice for use as a release modifier in formulations developed for prolonged release. The capacity of xanthan gum to form a gel upon hydration generates a diffusion barrier for the medication, which slows down the drug's release and contributes to the extended-release profile that is sought. As an additional benefit, its mucoadhesive characteristics improve the adherence of tablets to the mucosa of the gastrointestinal tract, which in turn extends the duration of the drug's residence time and enhances its absorption.

Guar gum, which is a galactomannan that is extracted from the seeds of Cyamopsis tetragonoloba, is yet another natural polymer that also has the potential to be used in formulations that provide prolonged release. The ability of guar gum to create a viscous gel, which in turn influences the release of the medication from the tablet matrix, is influenced by the high molecular weight of guar gum as well as its capability to facilitate hydration. The versatility of guar gum as a release modifier is due to the fact that it is compatible with a wide range of APIs and other excipients. Additionally, it has been observed that guar gum may have potential therapeutic advantages, such as its hypocholesterolemia and hypoglycemic effects. These effects may complement the therapeutic activity of losartan potassium in some patient groups for whom it is administered. In extended-release formulations, the combination of xanthan gum with guar gum in a synergistic manner may help solve some of the issues that are related with the kinetics of drug release. Formulators are able to establish a more exact control over the release profile by mixing these polymers, which allows them to optimize medication delivery for superior therapeutic effects. When it comes to customizing the release kinetics to the particular needs of the medicine and the therapeutic impact that is intended, the selection of optimum ratios of xanthan gum to guar gum is of the utmost importance. When it comes to the design and development of a successful drug delivery system, having a detailed understanding of the release kinetics of extended-release tablets is of the utmost importance. The release profile is affected by a number of parameters, including as the concentration of the polymer, the composition of the tablet, and the physicochemical characteristics of the medication. In order to shed light on the release mechanism and kinetics of pharmaceuticals that are derived from extended-release formulations, mathematical models are often used. Some examples of these models are zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. First-order kinetics entails a proportionate drop in drug concentration, Higuchi model provides a square root of time-dependent release, and Korsmeyer-Peppas model represents drug release from polymeric matrices. Additionally, zero-order kinetics means that the rate of drug release remains constant throughout time. The formulation and the unique properties of the medicine both have a role in determining which model is the most suitable among the available options. With regard to the extended-release tablets of losartan potassium that include xanthan gum and guar gum, it is essential to have a thorough grasp of the release kinetics in order to guarantee a therapeutic effect that is both prolonged and under control. An important step forward in the field of pharmaceutical research is represented by the creation of extended-release tablets of losartan potassium that include xanthan gum and guar gum as release modifiers. It is not only that this novel formulation overcomes the limits of traditional dosage forms, but it also has the potential to give therapeutic benefits. The continuous release of losartan potassium that is accomplished via the strategic use of xanthan gum and guar gum results in a more stable plasma concentration. This, in turn, minimizes fluctuations and reduces the possibility of adverse effects that are associated with peak medication levels.

Additionally, the use of xanthan gum and guar gum into the formulation may provide additional benefits, in addition to the immediate benefits that are associated with the kinetics of drug release. The mucoadhesive qualities of these polymers have the potential to increase the amount of time that the tablets spend in the gastrointestinal tract, which might lead to an increase in both the drug's absorption and its bioavailability. In addition, the fact that guar gum is compatible with a number of different medications brings to light the possibility that it may contribute to the overall therapeutic impact of the formulation. This is especially true in patients who have comorbidities such as diabetes or hyperlipidemia. One of the most exciting developments in the field of pharmaceutical research is the introduction of extended-release tablets of losartan potassium that include xanthan gum and guar gum as release modifiers. The painstaking formulation, which takes into consideration the distinctive qualities of xanthan gum and guar gum, provides a regulated and prolonged release of the medicine, therefore eliminating the constraints that are associated with traditional dosage forms. The use of these natural polymers in a synergistic manner not only improves the kinetics of drug release, but it also paves the way for the possibility of additional therapeutic effects that go beyond the core action of losartan potassium. When it comes to the management of hypertension and other disorders that are connected to it, extended-release tablets that include xanthan gum and guar gum open the way for better treatment results and increased patient compliance. This is because the research that concerns pharmaceutical formulation is always evolving.

II. REVIEW OF LITERATURE

Gunda, Raghavendra&Manchineni, Prasada. (2019). Using HPMCK100M as a release retardant, the current research study aimed to generate sustained release (SR) tablet formulations for losartan potassium. The formulations were intended to be used for the treatment of the condition. Techniques: An antihypertensive medication known as losartan potassium is classified as an angiotensin-II receptor blocker, which is a BCS class-II therapeutic agent. Through the use of the direct compression technique, SR tablets for Losartan Potassium were created by combining varying amounts of HPMCK100M and Xanthan Gum. The amounts of polymers were selected as independent factors, X1 and X2 respectively. On the other hand, the time necessary for dissolution of 10% (t10%), 50% (t50%), 75% (t75%), and 90% (t90%) of the medication from the formulation was selected as the dependent variables. There were nine different formulations that were produced and put through a series of pharmacopoeial testing. All formulations were determined to be within the allowed limits, and the release rate profiles of all formulations were fitted to kinetic models. The findings indicate that all formulations adhere to the acceptable limits. A determination was made on the statistical parameters. In order to account for dependent variables, polynomial equations were devised. It was determined whether or not they were valid by using countercheck formulations (C1, C2). A formulation (F4) that included a blend of 10% HPMCK100M and 14% Xanthan gum was found to be an identical formulation (dissimilarity factor f1 = 1.765, similarity factor f2 = 86.735) to the product that was being sold (COZAAR). This was determined in accordance with the recommendations provided by SUPAC. First order kinetics, often known as non-Fickian diffusion anomalous transport, is an approach that Formulation F4 takes. n equals 0.825.

Dhobale, Avinashet al., (2018) this study effort was conducted with the intention of formulating and developing a fixed dose combination product in two distinct strengths, utilizing the same blend for both strengths of tablet as a formulation for SR tablets. The Extended Release layer of the tablet is composed of an antihypertensive drug that belongs to the family of β-selective adrenergic blocking agents. It does not possess any features that are comparable to partial agonists or membrane stabilizing agents. Preparation with extended release allows for continuous release and lessens the likelihood of experiencing adverse effects that are difficult to manage. This medication is utilized in the treatment of hypertension and congestive heart failure in some instances since it is available in an extended-release formulation. This medication has been found to have a positive effect as an extended release

preparation, according to the clinical investigations. The primary purpose of the current research was to create, construct, and assess a matrix tablet by making use of hydrophilic natural retardant polymers. This tablet would be designed to delay the release of the medication in the upper gastrointestinal system, and it should begin to release the drug once it enters the alkaline environment of the small intestine. Both xanthan gum and metolose 90 sh were studied as potential candidates for the role of model hydrophilic retardant polymers. The production of sustained release matrix tablets was accomplished by the use of the wet granulation process. There were nine different batches of tablets made. Both pharmacopoeial and non-pharmacopoeial assessment criteria were used to the tablets that were manufactured. These parameters included loose and tapped bulk density, compressibility index, hausner ratio, angle of repose, friability, hardness, thickness, weight variation, percentage of drug content, and in-vitro drug release tests.

Gunda, Raghavendra &. A, Vijayalakshmi. (2018). the current study inquiry was conducted with the intention of developing sustained release (SR) formulations for losartan potassium by using 32 different factorial designs. Techniques: An antihypertensive medication, a non-peptide angiotensin-II receptor (type AT1) blocker, and a BCS class-III agent, losartan potassium is a combination of these three properties. Through the use of the direct compression method, SR tablet formulations of losartan potassium were created by combining varying amounts of hydroxyethyl propyl cellulose (HPMC) K100M and xanthan gum in various combinations. The number of polymers, HPMC K100M, and xanthan gum that were necessary to produce the drug release was chosen as the independent variable, X1 and X2, respectively. On the other hand, the length of time that was required to release 10% (t10%), 50% (t50%), 75% (t75%), and 90% (t90%) of the drug from the formulation was chosen as the dependent variable. In order to conduct a variety of pharmacopoeial experiments, nine different formulations were developed and analyzed. All of the formulations were determined to be within the pharmacopoeial limitations, and kinetic modeling was performed on the in vitro drug release patterns of each and every formulation. The findings of the study are shown below. There was a determination made about the statistical parameters, which included the intercept, slope, and correlation coefficient. In order to account for dependent variables, polynomial equations were devised. The validity of the polynomial equations that were generated was examined by developing two checkpoint formulations, which were designated as C1 and C2. The formulation (F4) that contains a blend of 15% HPMC K100M and 20% xanthan gum is the formulation that is the most comparable to the marketed product (LOSACAR) (similarity factor f2 = 86.747, dissimilarity factor f1 = 1.760, and no significant difference, t = 0.0477), as stated by the criteria provided by SUPAC. Concluding remarks: It was discovered that the mechanism of drug release is non-Fickian diffusion anomalous transport (n = 0.825), and the Best Formulation F4 adheres to the first-order, Higuchi kinetics.

Viswanath, V et al., (2014) Losartan potassium is a medication that is used to treat hypertension, and the purpose of this research was to produce a sustained release matrix tablet formulation of the medication. A variety of drug and polymer ratios were used in the formulation of the sustained release tablets, which were made by the process of wet granulation. Some examples of hydrophilic natural polymers that were used include xanthan gum (XG), guar gum, and cellulose. Investigating the drug's compatibility with a number of different excipients was done. Following an evaluation, it was determined that the compressed pills were in accordance with the Pharmacopoeial limitations. Tablet qualities that were deemed acceptable and in vitro drug release were taken into consideration while formulating the second formulation (F2). The formulation that was developed as a consequence generated matrix tablets that had the highest possible level of hardness, constant weight homogeneity, and friability. For losartan potassium, all of the tablets, with the exception of one, demonstrated progressive and near-complete sustained release, and 90.88% of the pills were released at the end of 12 hours. According to the findings of the dissolving trials, formulation F2 (drug to polymer 1:2) was the most effective of the investigation. It displayed a drug release pattern that was very similar to the

predicted release profile. When the polymer ratio was increased, there was a corresponding drop in the release kinetics of the product. All of the formulation tablets, with the exception of F2, exhibited diffusion-dominated drug release when used in conjunction with the exponential equation. The medication was released from F2 by a process that included diffusion in conjunction with erosion.

Vohra, D et al., (2012) Losartan potassium is an angiotensin II receptor antagonist that is easily absorbed from the gastrointestinal tract (GI tract) after being taken orally. Since it goes through a significant amount of first-pass metabolism and has a short elimination half-life, its bioavailability is lower than average. In the current work, the objective was to investigate the sustained release behavior of the medication by using both hydrophilic and hydrophobic polymers, and to optimize the process by employing a three-two complete factorial design. Both Eudragit and HPMC were used in order to assess the impact that hydrophilic and hydrophobic polymers have on the release pattern of the medicine inside the body. In order to determine the release behavior, a complete factorial was carried out with hydrophilic polymer concentrations of 20, 30, and 40%, as well as hydrophobic polymer concentrations of 2.5, 5, and 7.5%. An investigation of the process factors was carried out, and the findings demonstrated an exceptional flexibility in terms of drug release over extended periods of time. Taking into consideration the findings, it was determined that it would be appropriate to create a dosage form by using the optimal concentration of hydrophobic polymer in conjunction with hydrophilic polymer in order to alter the release behavior for more than twelve hours.

Azharuddin, Mohdet al., (2011) with the use of both natural and synthetic polymers, the purpose of this research is to create controlled release matrix tablets containing losartan potassium and then analyze their effectiveness. Different drug: polymer concentrations were used in the preparation of tablets, which were made utilizing the direct compression technique. According to the findings of a research that used differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FT-IR), there was no chemical interaction between the medication and the polymers that were utilized. For the pills, both the precompression and post compression parameters were in accordance with the pharmacopoeial limit specified. Following the completion of in-vitro release investigations, the findings reveal that the matrix tablet (F9), which has a combination of natural and synthetic polymer that is fifty percent by weight, exhibits superior controlled release over a period of twenty-four hours.

Patel, Viral & Patel, Natavarlal. (2007). Through the use of a factorial design technique, the current inquiry investigated the utilization of xanthan gum and guar gum for the creation of a floating drug delivery system for dipyridamole. Both the proportion of xanthan gum to guar gum (X(2)) and the amount of polymer blends (X(1)) were chosen to serve as independent variables. It was decided to use the diffusion exponent (n), the release rate constant (k), and the percentage of medication that was released after one hour (Q(1)) and six hours (Q(6)) as dependent variables. The buoyancy qualities that were wanted were present in tablets of all batches. With the use of a two-way analysis of variance (ANOVA), multiple regression analysis demonstrated that both of the covariates had a statistically significant impact on the response that was investigated ($p<0.05$). According to the findings of the Tukey test, the relative contribution of each level of the many components to the response that was investigated was shown. When compared to the content of polymer blends, it was determined that the ratio of xanthan to gur gum played a regulating impact on the kinetics of drug release that was either equivalent to or more dominating than the amount of that blend.

III. RESEARCH METHODOLOGY

It was a complimentary sample of losartan potassium that was received from ZydusCadila, which is located in Ahmedabad, India. Signet Chemical Corporation Pvt. Ltd. provided a gift sample of Xanthan gum (Xantural® 75) and polyvinylpyrrolidone K30 (Kollidon®30). Both of these products

were available for purchase. Lactose monohydrate and guar gum were purchased from Altrafine Gums in Ahmedabad, India, and SD Fine-Chem Ltd. in Mumbai, India, respectively. Both of these companies are located in India. In addition, all of the other components that were used were of an analytical quality and were obtained from SD Fine-Chem Ltd. in Mumbai, India.

IV. DATA ANALYSIS AND INTERPRETATION

Preparation of extended-release tablets

Wet granulation was the procedure that was used in the preparation of the 90 mg extended-release tablets of losartan. The amount of lactose monohydrate, xanthan gum, guar gum, and losartan that was weighed was passed through a sieve with a mesh size of sixty on each side. A method known as geometric dilution was used in order to combine the components. Using a suitable amount of a polyvinylpyrrolidone solution that had been produced in isopropyl alcohol, granulation was carried out after the blending process was completed. The moist material was first filtered through a sieve with a 12-mesh opening, and then the granules were dried in an oven at a temperature of 40 degrees Celsius for a period of ninety minutes. After that, the granules were put through a filter with a 25-mesh opening. After mixing for three minutes, the granules were finally lubricated with a mixture consisting of 1% magnesium stearate, 1% talc, and 1% aerosil. In order to compress the granulation mix of the extended release tablet into tablets, a rotary tablet compression machine (Karnavati) was used, along with punches and a circular die measuring 10 millimeters in diameter.

Optimization study using DoE (Design of experiments)

The formulation optimization was carried out by using the D-optimal mixture design technique with the assistance of the Design-Expert program. Three independent variables and four dependent variables were chosen. The quantity of xanthan gum (A), guar gum (B), and lactose (C) were chosen to be the independent variables. Additionally, the limitations that were put on the cumulative total of all independent variables, the total amount of gum, and the ratio of the gums were also considered. It was decided to use the following response variables: % release at 1 hour (Y1), 4 hours (Y2), 7 hours (Y3), and 10 hours (Y4). Table 1 displays the independent variables, as well as the constraints and dependent variables, as well as the criteria that have been established for numerical optimization.

Table 1: Variables in D-optimal mixture design for losartan 90 mg tablet formulation

Independent variable	**Lower limit (mg)**	**Upper limit (mg)**
A: Xanthan Gum (X_1)	1.948	16.248
B: Guar Gum (X_2)	4.835	26.01
C: Lactose (X_3)	179.45	202.3
Constraints Set for the independent variables 9.75 ≤ Xanthan Gum+Guar Gum		≤ 32.3
0.25 ≤ Xanthan Gum/Guar Gum		≤ 1
Xanthan Gum+GuarGum+Lactose = 212.250 Dependent variables with their criteria for optimization Percent release in 1 h (Y_1)		12-14
Percent release in 4 h (Y_2)		40-42
Percent release in 7 h (Y_3)		66-68
Percent release in 10 h (Y_4)		82-88

As can be seen in table 1, there are three independent variables (X1, X2, and X3) that are stated with their respective lower and higher bounds. These variables indicate the amounts of Xanthan Gum, Guar Gum, and Lactose, respectively. For X1 (Xanthan Gum), the dosage varies from 1.948 to 16.248 mg, for X2 (Guar Gum), the dosage ranges from 4.835 to 26.01 mg, and for X3 (Lactose), the dosage ranges from 179.45 to 202.3 mg.

The restrictions for these variables are stated as follows: the entire amount of Xanthan Gum, Guar Gum, and Lactose should equal 212.25 mg, the ratio of Xanthan Gum to Guar Gum should be within the range of 0.25 to 1, and the sum of Xanthan Gum and Guar Gum should both lie within the range of 9.75 to 32.3 mg collectively.

The dependent variables for optimization include the percentage of release at different time intervals (Y1-Y4): 12-14% in one hour, 40-42% in four hours, 66-68% in seven hours, and 82-88% in ten hours. These parameters provide a suggestion for the release profiles that are wanted for the chemical or pharmaceutical procedure that is being investigated. Providing a thorough framework for optimizing the formulation based on the provided variables, the defined constraints and dependent variable criteria offer a comprehensive framework for optimizing the formulation. This framework ensures that the required release profiles are obtained within the set limitations.

Model fitting of the drug release data

Additionally, the slope of the Korsmeyer–Peppas model is shown in table 2, along with the regression coefficients for a number of other models. It was indicated by the regression coefficients for the different plots of all the validation batches that the release data exhibited the best fit in zero. The model fitting of the drug release data order model is shown in Table 2. The fact that the value of slope in the Korsmeyer-Peppas equation was found to be greater than 0.89 for each of the three batches provides evidence that case-II transport is the mechanism that is responsible for the release of the medication. The zero order release kinetics are followed by the transport in Case II. According to the Korsmeyer-Peppas equation, the release data likewise follows zero-order kinetics. This is the conclusion they reach.

Table 2 Model fitting of drug release data

batches	First order ln m = kt	Higuchi m0-m = kt1/2	Zero order m0-m = kt	log (m0-m) = log K+n log t
LT-1	0.9771	0.9578	0.9920	0.9078
LT-2	0.9743	0.9508	0.9913	0.9520
LT-3	0.9659	0.9570	0.9918	0.8950

The provided table 2 presents data for different batches labeled LT-1, LT-2, and LT-3, along with corresponding values for four different kinetic models used in drug release studies. The first column represents the batches, while the subsequent columns provide values for the first order ln m = kt, Higuchi model m0-m = kt1/2, zero order m0-m = kt, and the logarithmic form log (m0-m) = log K + n log t.

In the first-order kinetics, represented by ln m = kt, the values range from 0.9659 to 0.9771 across the batches. For the Higuchi model, m0-m = kt1/2, the values range from 0.9508 to 0.9578. The zero-order kinetics model, m0-m = kt, shows values ranging from 0.9913 to 0.9920. Lastly, the logarithmic model, log (m0-m) = log K + n log t, varies from 0.8950 to 0.9520.

These values suggest variations in the drug release kinetics across the different batches, indicating potential differences in the release mechanisms or rates. The interpretation of these results would depend on the specific context of the drug delivery system being studied, with each kinetic model providing insights into different aspects of the release process. Further analysis and consideration of the system under investigation would be necessary to draw more detailed conclusions about the drug release behavior in each batch.

V. CONCLUSION

The creation of extended-release tablets that include losartan potassium and release modifiers such as xanthan gum and guar gum marks a major step forward in the field of pharmaceutical innovation. Because of the thorough formulation, the limitations of traditional dosage forms are addressed, and the medicine is released in a regulated and sustained manner. Xanthan gum and guar gum have

synergistic qualities that not only optimize the kinetics of drug release but also provide possible therapeutic advantages. These benefits include increased patient compliance and enhanced treatment results. As research in the pharmaceutical industry continues to advance, these extended-release tablets provide a potential avenue for the successful treatment of hypertension and other disorders associated to it. This highlights the continued dedication to enhancing medication delivery methods in order to provide the best possible care to patients.

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