



International Journal of

Innovative Drug Discovery

www.ijidd.com

e ISSN 2249 - 7609
Print ISSN 2249 - 7617

FORMULATION AND EVALUATION OF MEDICATED CHEWING GUM OF HYDROXYZINE

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ABSTRACT

Medicated chewing gums have become an alternative oral drug delivery system in response to their promise of ease of use, increased patient compliance, and improved bioavailability. The purpose of this study was to develop and test medicated chewing gums with Hydroxyzine hydrochloride, an antihistamine that is used to treat anxiety, nausea, and motion sickness. Pharmagum M was used as the gum base, and hydroxyzine was loaded into the matrix base of the gum, with different excipients to enhance the release of the drug. The formulations were evaluated on organoleptic properties, pre-compression, and post-compression properties such as drug content, hardness, friability and in vitro drug release. The findings showed that the formulations were able to give a controlled and sustained release of Hydroxyzine with formulation MCG4 having the best release of the drug (95.88%) in 30 minutes. The paper also noted the effect of gum base and magnesium stearate on drug launch rate. The stability analyses indicated that MCG4 had preserved its physical and chemical stability during accelerated storage environments. The results indicate that medicated chewing gums serve as a viable and patient-friendly alternative to traditional forms of oral medication, and improved therapeutic benefits could be realized by the use of medicated chewing gums in the management of acute disorders such as anxiety and nausea.

KEY WORDS: Medicated chewing gums, Hydroxyzine hydrochloride, sustained release, formulation development, in vitro release, stability testing.

INTRODUCTION

Medicated chewing gums are a new and promising alternative to conventional oral delivery systems of drugs e.g. tablets and capsule [1]. These gums have a range of benefits such as ease of use, enhanced patient compliance, and bioavailability. They are especially useful when the patient finds it hard to swallow pills, like children, the elderly, or bedridden patients. Medicated chewing gums in contrast to the traditional oral drug types have active pharmaceutical ingredients (APIs) that are deposited immediately in the buccal mucosa to avoid the gastrointestinal (GI) tract and first-pass metabolism in the liver. This leads to an increase in absorption rate and rapid action onset thus enhancing the therapy outcomes. The ability to release drugs in a sustained manner is one of the most important advantages of medicated chewing gum [2]. A gum matrix is built to regulate the delivery of the API, big therapeutic effect and fewer dosing. Moreover, chewing also activates the production of saliva, which increases the

rate at which the drug gets absorbed in the oral mucosa. The mechanism permits the drug to take a faster action than the traditional oral tablets or capsules, particularly when a quick effect of the drug is needed, such as an anti-anxiety or anti-nausea drug [3]. Also, medicated chewing gums are patient-friendly and easy to consume, which is why they are suitable in cases of chronic disease where adherence is important. The fact that medication can be taken as a gum, as well as the option to make the gum taste, feel, and release at a particular rate, also emphasizes patient satisfaction and stimulates regular use of prescribed remedies [4]. This flexibility is especially useful when working with patients with particular needs or preferences, where they can follow the drug regimens they are prescribed.

Controlled and Sustained Release of Hydroxyzine

The extended release of hydroxyzine is one of the major benefits of placing the drug in medicated chewing gum. The gum matrix may be designed to regulate the rate

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of drug release so that hydroxyzine is slowly given out and assimilated as the gum is chewed. This controlled release ensures that the therapeutic level of the drug remains constant and stable over a longer period to lower the rate of administration and enhance patient compliance. The slow delivery also gets rid of the peak-and-trough effects which are so typical of standard dosing forms and causes therapeutic effects to be more stable [5]. Medicated chewing gum is especially useful in patients who are unable to swallow pills such as children, the elderly, or individuals with swallowing problems. The attractiveness of the chew, which could be flavoured to match the taste of the patient, is also a bonus, making it more acceptable and heightening the chances of compliance. Medicated chewing gum will help patients get the needed treatment in a convenient, efficient and easy-to-use manner, as an alternative to tablets and syrups.

Formulation Considerations for Medicated Chewing Gum Mediated chewing gums development:

The choice of gum base and excipients to provide the desired drug release profile and stability is made. The natural or synthetic resin, softeners, and fillers that form the gum base need to offer the right texture, elasticity and mechanical rigidity to enable the drug release over time [6]. To retain the active pharmaceutical ingredient (API), hydroxyzine in the gum matrix, the incorporation should be consistent to establish uniform distribution and stability to provide consistent dosing and efficacy. As a water-soluble drug, hydroxyzine can be added to the gum matrix as a solution or suspension to be dispersed uniformly and maintained stable. The reason why hydroxyzine dissolves fast in the saliva, and then is absorbed through the buccal mucosa, is its solubility. Factors that may affect the rate of release include: gum base composition, plasticizers and softeners, the fraction of active ingredient in the formulation.

Stability and Environmental Considerations

The most important aspect in the making of the medicated chewing gum is stability. Hydroxyzine, as is common with most medications, is temperature, humidity, and light sensitive, and can deteriorate with time. Preservatives and stabilizers can be included in the formulation to achieve stability of the medicated chewing gum. Further, the gum should be exposed to a range of storage conditions to ensure that it does not become ineffective as the shelf life progresses. Stability testing is the process that checks the physical appearance of the gum, the drug content and the release properties of the gum with time. This assists in establishing the shelf life of the product and has the benefit of providing the product with the same therapeutic effects during its shelf life. A stability test should be performed in order to determine the long-term efficacy and safety of the medicated chewing gum [7].

METHODOLOGY

PRE-FORMULATION STUDIES

Identification of Drug

Determination of organoleptic characteristics

By visual examination the drug was tested for its physical characters like color, odor and appearance.

Determination of Melting Point

The drug melting was ascertained by the capillary fusion technique. A capillary tube was capped at either end after which it was charged with a small volume of the drug. The capillary tube was subsequently inserted in an inverted manner into the melting point equipment with its closed end directed downwards. The thermometer provided was used in recording the temperature at which the drug melted.

Spectrometric Identification of Drug by using UV spectroscopy

Drug sample was taken 10 mg and then dissolved in 25 ml of absolute alcohol (ethanol) and volume adjusted to 50 ml by using phosphate buffer solution (PBS) pH 7.4. To a 10 ml volumetric flask 0.5 ml of this stock solution was put and the volume adjusted to 10 ml with PBS pH 7.4. The concentrations of these solutions have a drug of 10ug in one ml of pH 7.4 PBS [10µg/ml]. Lastly, the sample [10µg/ml] was scanned between 200-400 nm with UV - spectroscopy to arrive at the 1 max.

Pre-compression Characteristics

Bulk Density

It is a ratio between the mass of the powder as a whole to the bulk volume of the powder. The value was arrived at by weighing the powder in a measuring cylinder then noting the volume. It is measured in g/mL and is given as:

$$\text{Bulk Density} = \frac{\text{Weight of powder}}{\text{Bulk Volume}}$$

It is the ratio of the mass of the powder (total mass) and the tapped powder volume. The tap volume was ascertained by tapping the powder till a fixed volume was obtained. It is g/mL and its calculation is:

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped Volume}}$$

Compressibility index

Carr index of compressibility was applied to measure the compressibility index of the powder blend. A simple way of measuring the loose bulk density (LBD) and tapped bulk density (TBD) of a powder, in addition to its packing characteristics is through this test. Carr index formula, as below:

$$\text{Compressibility index} = 100 \times \left(1 - \frac{\text{Bulk density}}{\text{Tapped density}} \right)$$

Hausner's ratio

Using bulk density and tap density as a basis, it is calculated as follows:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of repose

These loose powder frictional forces may be measured through the angle of repose (theta). This is the angle that the surface of a pile of powder can measure against the plane of the guy. The mixture of the powder was put across a funnel which was connected on a stand at a stipulated height. The slope angle was then determined using the size of the resulting heap of powder which included the radius and its height.

Loss on drying

At 105°C and halogen moisture balance instrument, the loss on drying of the material was measured for 4 minutes.

Compatibility studies for drugs and excipients

Infrared (IR) spectroscopy was used to study the drug-excipient interaction studies. The pure drug and a solution of the drug together with excipients were added to KBr and pressed into pellets. These pellets were then inserted in the light path of the spectrometer and a spectrum recorded in wavenumber range of 4000-400 cm⁻¹. The analysis of IR spectra of the polymers (Eudragit RL 100 and Ethyl cellulose) free and incorporated in the drug was performed [8].

Formulation Development [9]

Conventional method

A conventional tableting technique has been used to manufacture MCGs using a conventional process that has been explored recently. Gum bases are dry powder mixtures that can be mixed directly with APIs and excipients to produce gum products (tablets) of the desired size and shape. The methods employed to manufacture and optimize the behavior of release of product are not thoroughly tapped and indulged into in regard to the methods used to manufacture and optimize the released behavior. A few research tasks are in progress to expand this platform to the extent of making it applicable to the delivery of drugs in a better manner and at a lower cost.

Each of the ingredients was weighed carefully according to the formula; weighed materials were passed in sieve no. 16 to help in reducing the size of the particles and placed aside. The flavor and aerosil were combined and then well-kept aside. Sorbitol, sucralose and the drug-pharmagum M were combined. Last of all, the weighted portions of the Magnesium stearate were added. Re-granulation was done by sieving the mixture in sieve no 30. These granules were weighed then we compressed them with a 14mm punch in rotary tablet punching machine. There were six sets of prepared formulations that were examined in the present study.

Characterization of prepared formulation

Friability Test

They are normally determined through their use of them friabilator. A random number of 10 tablets was taken, weighed and subjected to GO ON Friabilator through Veego friabilator.

$$\text{Friability} = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100$$

Weight Variation

Weight change test of the chewing gum was performed according to USP 20. The chewing gums were chosen at random, weighed, and the weight was noted. Mean weight was computed and the percentage deviation of each weight of chewing gum as compared to the mean weight computed.

Hardness test

The Monsanto hardness tester is used to gauge the resistance needed in order to crack the chewing gum.

Estimation of drug content

The chewing gums, unlike tablets, cannot be assayed by the conventional methods, which included the crushing of the tablet, calculation of the correct weight of the medicament, as well as the approximation of the content. The DRT 6 Chewing Apparatus manufactured by Erweka is a newly manufactured device that can simulate the natural chewing gums to estimate the amount of drug found in chewing gums and observe the process of the drug release. The composition of the elements that come to the direct contact with the chewing gum plays a significant role as to the functioning of the device. Acid-proof non-corrosive stainless steel is an unpolished surface that offers a jaw. In order to chew gum, the jaws are forced to hold tightly to the chewing gum due to the blasted surface. The perfection of jaw is based on the fact that your upper jaw stays in place against the lower in a way that it is attached against the vertical motion. It can however spin on its axis through a revolving system. The lower jaw is an up and down motion system with a linear/axial mechanism but is locked-out against rotational movement. The lower jaw moves indicating in the test cell. Chewing involves a combination of up and down movements of the lower jaw with a shearing (twisting) action of the upper jaw and enables the chewing gum to be adequately worked up and at the same time a proper agitation of the test medium. A lift device can be attached to the deformity called the lower jaw/test cell to be elevated or depressed. When dropped down into the lowest position, it is absolutely free-standing of the upper jaw and so it is easy to prepare it to analyse, samples, empty out and clean it after testing. This ceases the release of the drug during sampling as the mechanical processing and its mixing cease.

The lower jaw is also flat with the underside that is parallel to the middle of the lower jaw. The lower jaw has

the small brim in that it is inclined at an angle of 45 degrees that forms a small bowl with the flat bottom that does not allow the chewing gum to fall apart during mastication. Analysis in circular nets of inert polymer could be of use in keeping the chewing gum stable. Thermostatic test cell is a clear glass to enable physical check-up during testing. It is supplemented by a metal thermostat chamber which is in direct collaboration with the lower jaw. The upper jaw is left cold and it is connected to an axis that covers warmth. The heating of the water bath is done using a heater.

***In vitro* drug release [7]**

The apparatus was positioned and filled with 50 mL of SSF and inserted with a chewing gum. The equipment ran at an average of 50 strokes per minute of

chewing. Every 5, 10, 15, 20, 25 and 30 min thereafter, 5 mL of SSF was removed through test cell, and another 5 mL of fresh SSF supplemented into the test cell per each time of sample removal. withdrawal volume then was adjusted to 100 mL with SSF. The resulting solution was left to absorb the 232 nm.

RESULTS AND DISCUSSION

Pre-Formulation Studies

Identification of Drug

Determination of organoleptic characteristics of Hydroxyzine hydrochloride:

Its color, smell and physical look was checked and noted. Table 1 gives the results.

Table 1: Organoleptic characteristics of Drug

S. No	Characteristics	Observation
1	Colour	White
2	Odour	Odourless
3	Appearance	Crystalline powder

Determination of Melting Point

Melting point of hydroxyzine hydrochloride is identified and it is in table 2 given below by the capillary

fusion method

Table 2: Melting point of Drug

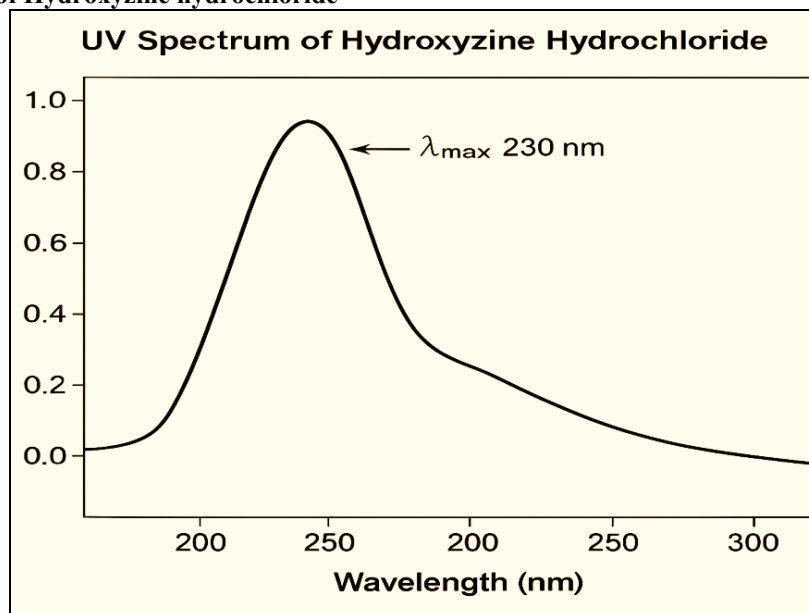
Drug	Melting Point °C (Literature)	Melting Point °C (Practical)
Hydroxyzine hydrochloride	190-192°C	189°C

The melting point of hydroxyzine hydrochloride was found to be 189°C. This value is same as that of literature value 190-192°C.

Spectrometric Identification of Drug by using UV spectroscopy

Absorption maxima (1 max) were found reasonably close to 232nm. UV spectrum depicted as in figure 1.

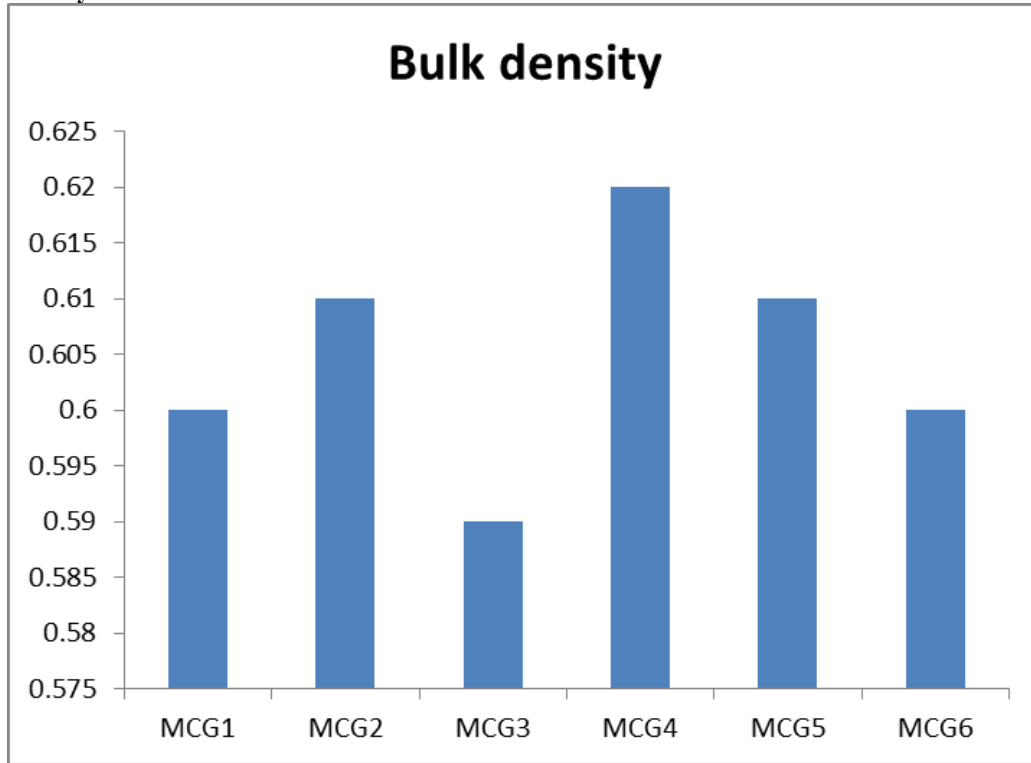
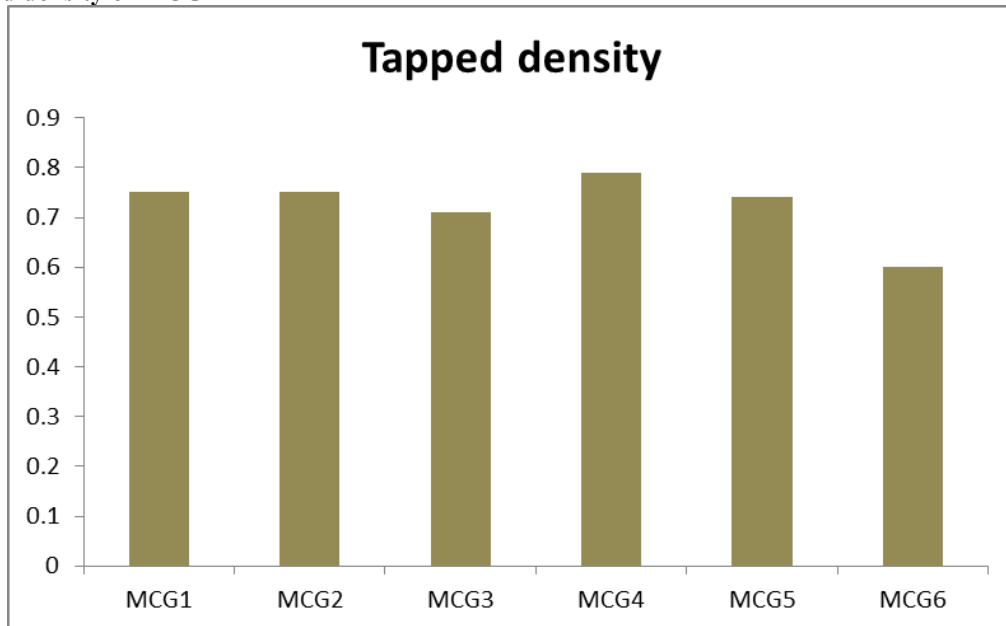
Figure 1: UV Spectrum of Hydroxyzine hydrochloride



Pre-compression Characteristics

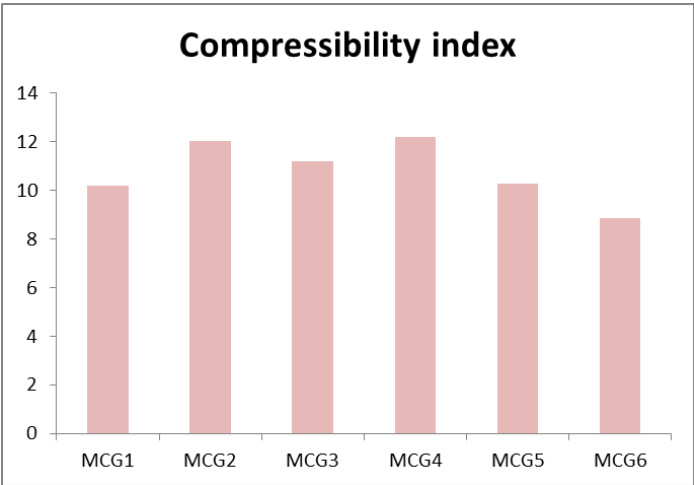
Other pre-compression properties of the powders were examined prior to the powder mass undergoing the process of getting punched into tablets and they included

bulk density, tapped bulk density, Carr compressibility index, angle of repose and loss on drying. These tests render the following results in the table below.

Bulk density**Figure 2: Bulk density of MCG****Tapped Density****Figure 3: Tapped density of MCG**

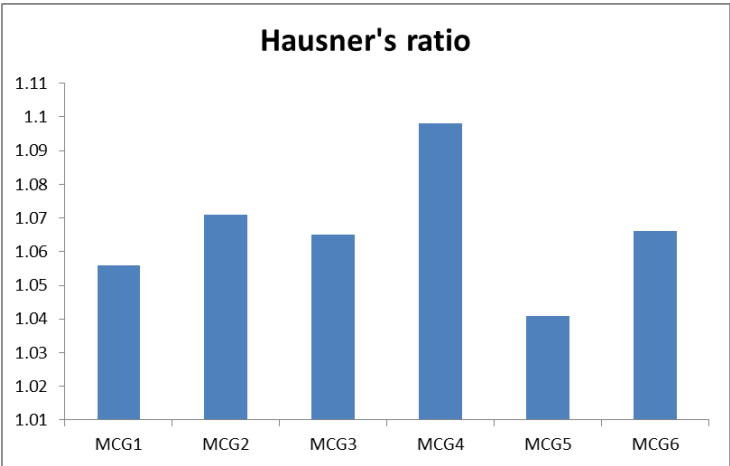
Compressibility index

Figure 4: Compressibility index of MCG



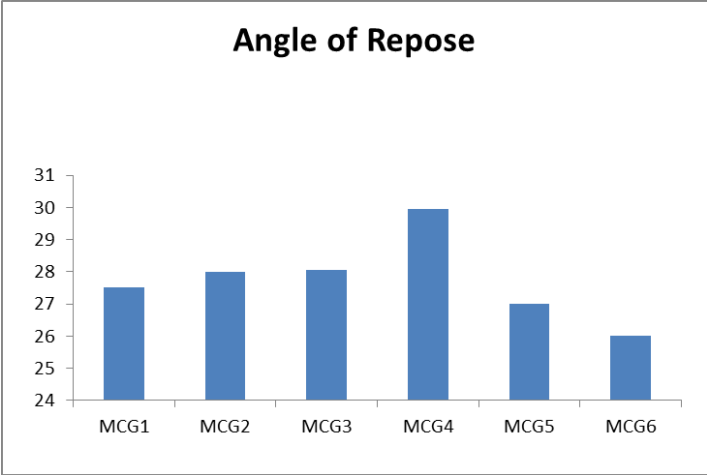
Hausner's ratio

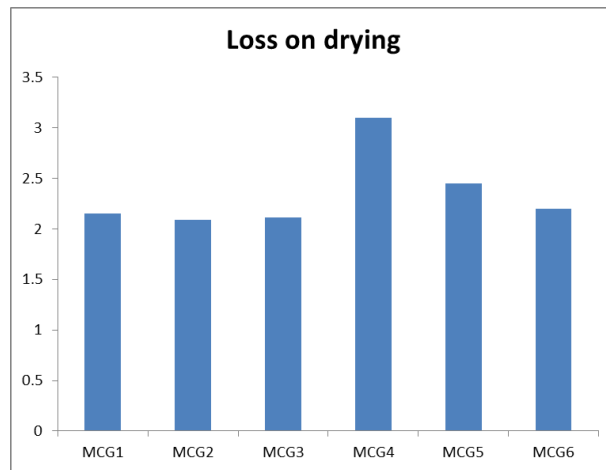
Figure 5: Hausner's ratio of MCG



Angle of repose

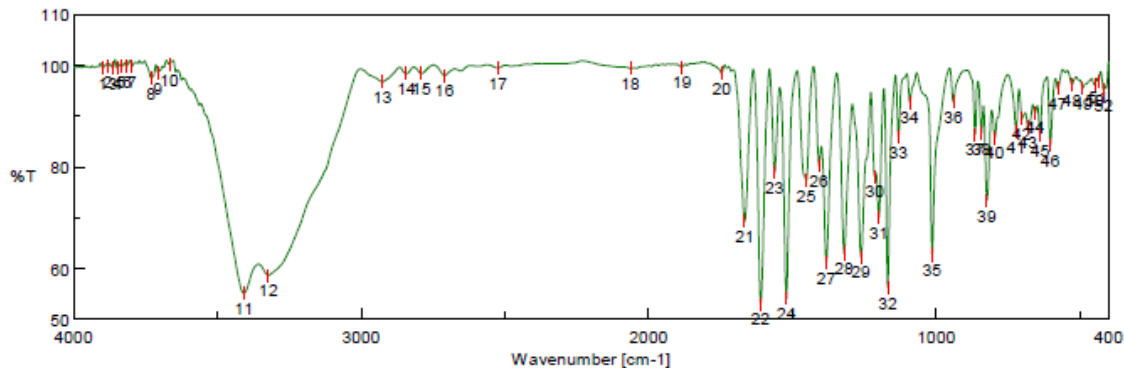
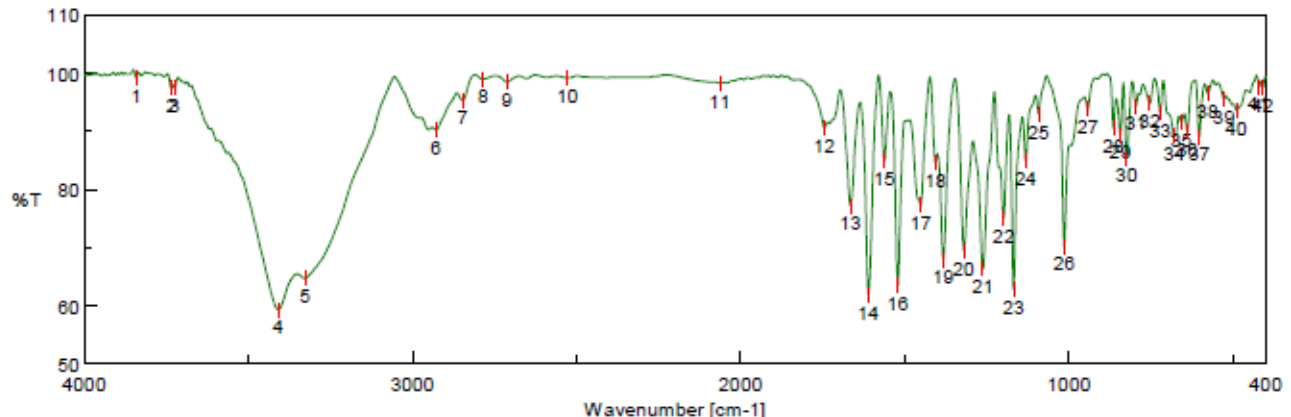
Figure 6: Angle of repose of MCG



Loss on drying**Figure 7: Loss on drying of MCG**

Based on the table, the bulk density of the drug in all formulation ranged between 0.59 to 0.62, the tapped density between 0.60 to 0.79, the compressibility index of car in all formulation was in the next range of 8 to 12 and Hausner ratio represented as 1.056 to 1.098. The formulation angle of repose was in the range of 29.95-26.

FT-IR spectroscopy-based drug-excipient interaction has been studied. The typical peaks in the FT-IR spectrum of the physical mixture of the hydroxyzine hydrochloride and the polymers did not shift and did not disappear. It means that the polymer did not have any interaction with hydroxyzine hydrochloride. The figure provides the IR spectrums of the pure drug and the physical mixtures, whereas a summary of the characteristic peaks.

Compatibility studies for drugs and excipients**Figure 8: IR Spectrum of Pure Drug****Figure 9: IR Spectrums of Pure Drug and Pharmagum M**

Formulation Development

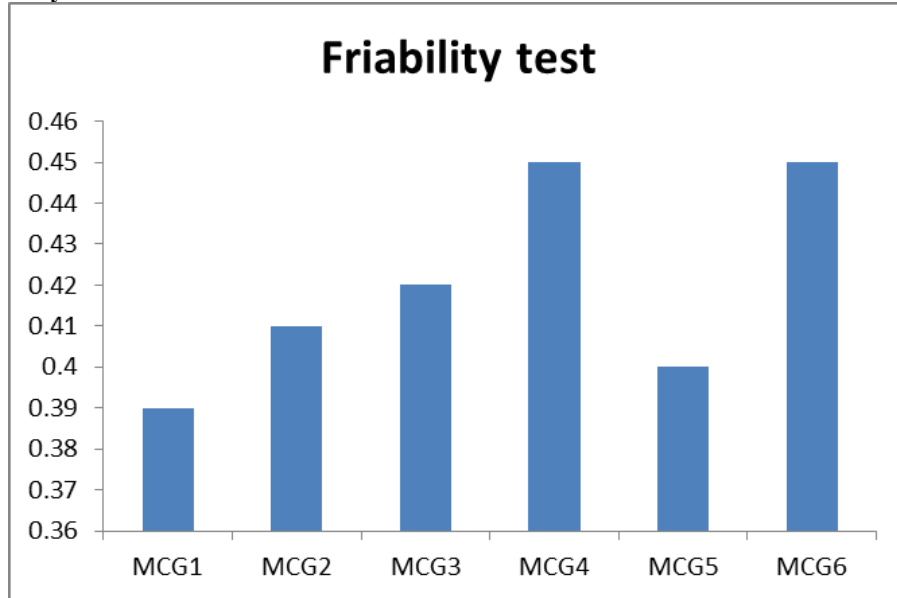
An easy conventional method was used to prepare six different formulations (F1-F6) of Hydroxyzine hydrochloride by the use of various polymers and in their different concentrations as well as the different plasticizers. The formulations were set and subsequently tested against several parameters, such as friability, weight variation, drug content estimation, chewing gum consistency, in vitro drug release and hardness.

Characterization of prepared formulation

Several parameters such as friability, test weight variation, hardness, estimated drug content, in vitro drug release and chewing gum consistency were tested in the prepared formulations. The findings are provided in the figures.

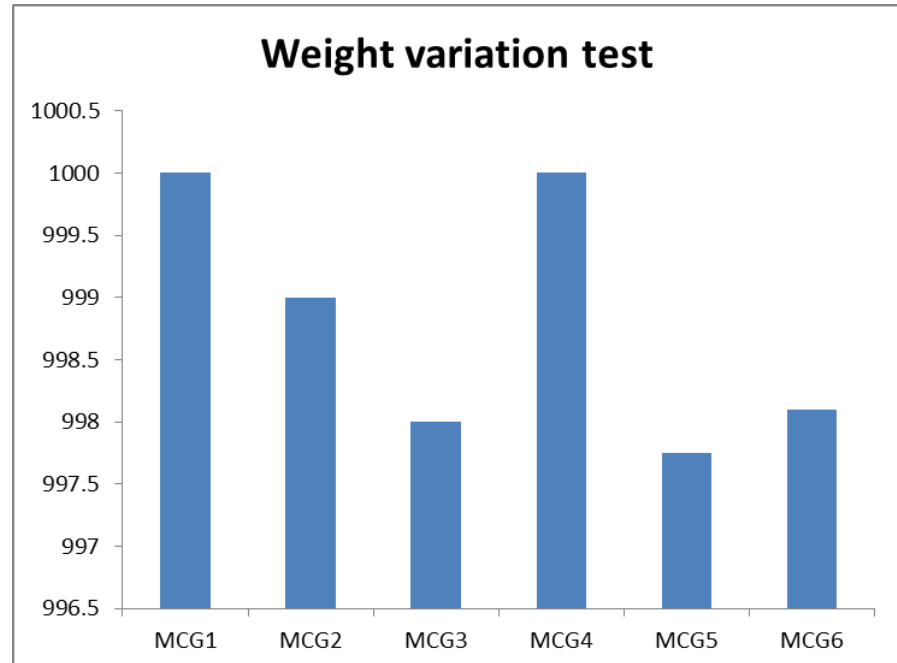
Friability Test

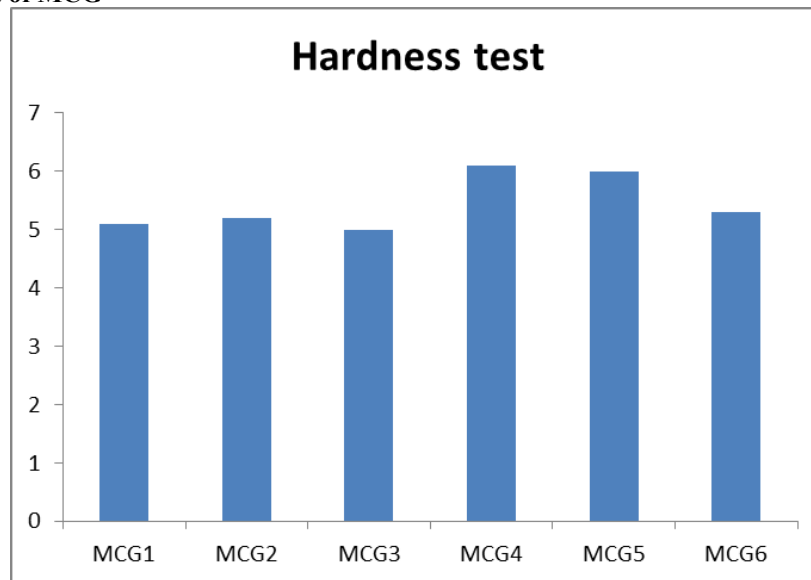
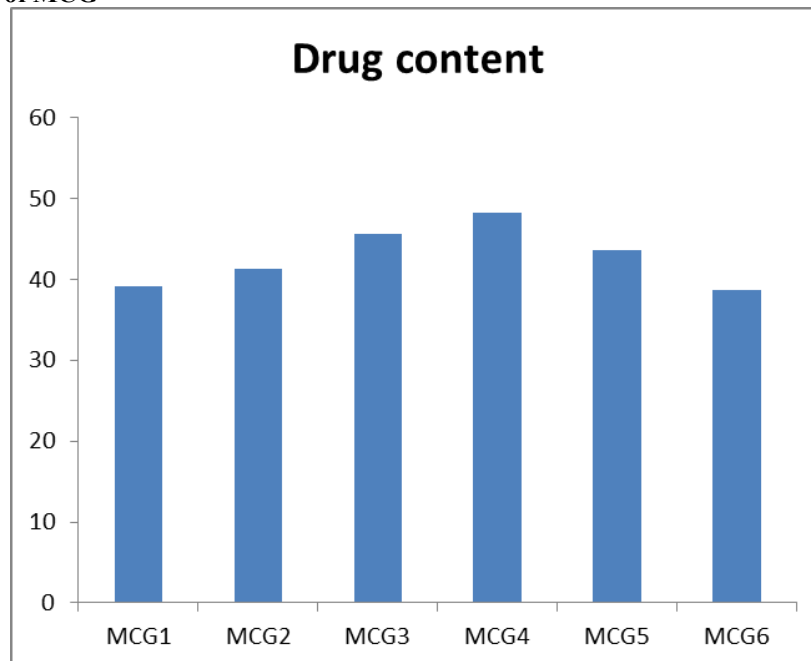
Figure 10: Friability study of MCG



Weight Variation

Figure 11: Weight variation test of MCG

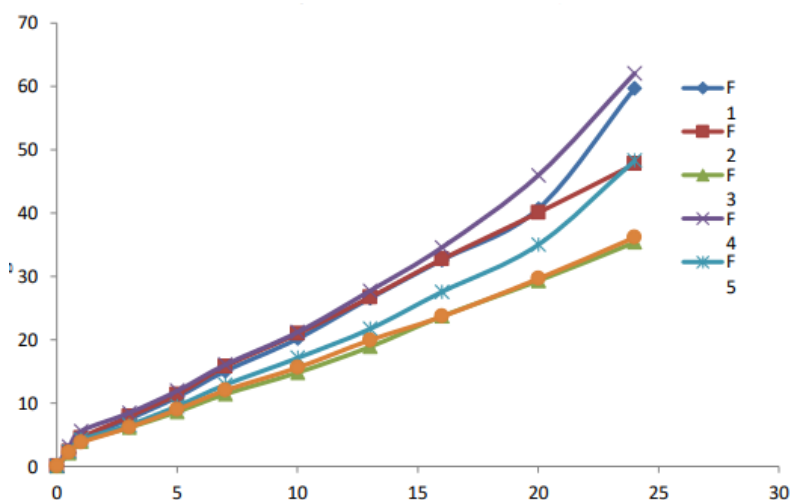


Hardness test**Figure 12: Hardness test of MCG****Estimation of drug content****Figure 13: Drug content of MCG**

The formulated product was tested on drug content which was within 38.68 to 48.19 mg of hydroxyzine hydrochloride per chewing gum. The drug content that appeared in the formulation of the highest content was found to be that of MCG4, with 48.19 mg of hydroxyzine hydrochloride per chewing gum, and the drug content that declined as it appeared in the least content was in MCG6, with 38.68 mg of hydroxyzine hydrochloride per chewing gum.

***In vitro* drug release**

The formulations prepared were investigated on in vitro drug release by the help of Erweka, DRT 6, Chewing Apparatus. During the study, the simulated salivary fluid was used as the dissolving medium, the length of the study was 30 minutes and the frequency of chewing was a factor of 50 strokes in 1 minute. The drug release caused by formulation MCG4 was biggest (95.88%) at the end of 30 minutes, whereas, the drug release caused by formulation MCG6 was the lowest (38.75%) at the same time.

Figure 14: Dissolution profile of F1 to F6 of MCG

DISCUSSION

In the present study an attempt was made to formulate medicated chewing gum containing Hydroxyzine hydrochloride using Pharmagum M as the gum base. Hydroxyzine prevents nausea and vomiting by reducing the activity of the center in the brain that controls nausea [12]. It also prevents motion sickness by reducing excitability of neurons in the motion and balance center (vestibular region) of the brain.

Hydroxyzine has not any disagreeable taste and it is not irritant to mucosa. The drug has below 100 μ m particle size and suitable pKa for mucosal absorption. Chewing gum formulation obtains fast/rapid onset of action, high bioavailability, pleasant taste, ease of administration without water, promotes higher patient compliance, reduce side effects, product distinctiveness from a marketing perspective, Excellent for acute medication, Counteracts dry mouth [13]. Pharmagum M and Magnesium stearate provides better chewing gum consistency to the medicated chewing gum. Influence of gum base and magnesium stearate, the dissolution profile of the drug varies depending on the content of gum base and magnesium stearate contained in the formulation. The findings established that drug release of the formulation is enhanced with an increase in gum base [14]. To decide the shelf life and condition of storage of the formulations Accelerated stability studies was done on MCG 4 formulation in Remi Stability chambers.

Various parameters such as physical appearance: No change, hardness: $6.102.45 \pm 6.202.28$, friability: $0.450.02 \pm 0.480.06$, weight variation: $10001.4 \pm 1000.40.80$, drug content: $96.3096.36$ and drug release profile: $95.082.21 \pm 95.352.42$. The comparative results were that in results the formulations MCG3 and MCG5 exhibited good drug release rate but these formulations did not exhibit good chewing gum like consistency. However formulation MCG4 has been more encouraging in delivering the drug at the necessary rate and then they bring with them the convenience of the chewing gum like consistency. Still

formulation MCG1, 2 and 6 does not release much drug and neither does it have appropriate chewing gum suspension. MCG 6 sticking problem is because of the amount of gum that is too large. It is observed that the concentration of the gum base and magnesium stearate held in right proportion than drug release is maximum. In this way, one may say that by modulating the quantity of gum base and magnesium stearate in the composition it is possible to regulate the release of the drug. In this manner we have been able to develop medicated chewing gums carrying hydroxyzine hydrochloride. With increase in concentration of gum (surpassing the adequate quantity) we can retard the release of drug i.e. we can maintain the release of drug. However, when we add more gum it brings about trouble during compression. In this instance, the gum will adhere on the punches and dies. Thus, MCG 6 formulations cannot be made in large size batch. According to the research, drug release of the chewing gum can be regulated to the target pace and simultaneously neutralize the slight bitterness of drugs by altering parameter such as gum base and soya powder concentration.

CONCLUSION

Finally, the chewing gum preparations of hydroxyzine hydrochlorate have demonstrated to be potential in terms of sustained and moderate drug release, patient compliance, and bioavailability. The experiment enabled us to confirm that the concentration of gum base and the excipient concentration, specifically, Pharmagum M, and magnesium stearate are useful variables influencing the profile of release and chewing consistency. The preparations containing MCG4 had already displayed excellent drug delivery potential and excellent physical properties and have shown that medicated chewing gums could be regarded as an alternative to improve therapeutic results even in patients that might have to be able to achieve rapid improvement of symptoms.

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