International Journal of Pharmaceutical Development & Technology

www.ijpdt.com

e ISSN - 2248 - 910X

Print ISSN - 2248 - 9096

A NOVEL GUM-BASED ANTI - EMETIC DRUG DELIVERY SYSTEM CHEWING GUM

Tanam. Srikala*, Purushothaman M

KLR Pharmacy College, Paloncha, Bhadradri Kothgudadm, Telangana- 507511, India.

ABSTRACT

Therapeutic drugs must be delivered via a mechanism that is both efficient and secure. An ideal DDS would have the following characteristics: bioavailability, regulated drug delivery to the body, ease of administration, and cost-effectiveness. Medicated chewing gum should be chewed for a certain period of time to deliver the dose, and then discarded. The IR spectrum of Pure Drug and Physical mixtures was shown in Figure and Characteristics peaks are summarized. The formulation MCG4 was more promising in delivering the drug at required rate and at the same time they maintain the chewing gum like consistency.

Keywords: Buccal, Hydroxyzine Hydrochloride, Chewing gum, Medicated Gum.

INTRODUCTION

Creating innovative technologies that will provide formulations unique properties to get around the therapeutic constraints of conventional dosage forms is a big challenge in pharmaceutical development. These encompass flexible use, carrying numerous active ingredients, adjusting release profiles, improving patient accessibility, and compliance. Therapeutic drugs must be delivered via a mechanism that is both efficient and secure. An ideal DDS would have the following characteristics: bioavailability, regulated drug delivery to the body, ease of administration, and cost-effectiveness. The medications can be administered using a variety of dose forms, including pills, capsules, lotions, ointments, and injections. Innovative techniques and new dosage forms make up the Novel Drug Delivery System (NDDS). It maintains the concentration of the drug for a longer period of time through the use of novel drug delivery systems [1].

Advanced Treatment for Drugs By Buccal Administration

It has been noted that oral administration through skin and mucosa has the potential to bypass the hepatic first pass metabolism. It is believed that different mucosal surfaces in the body act as absorption sites for drugs, depending on their location in the body.

Types of CG

- Due to its wide range of applications, chewing gum is being manufactured in many shapes and sizes (cubes, balls, oval shapes, and strips) as well as flavours (mint, strawberry, orange, mango etc.) and there is no standard size and shape. Basically, chewing gum consists of a gum base and a water-soluble phase of sweeteners, flavours, food colors, and active pharmaceutical ingredients [2].

MEDICATED CHEWING GUM

The European Pharmacopoeia as well as the Council for Drugs for Human use for dosage forms for pharmaceuticals from 1991 defines a medication chewing gum as a solid single dose formulation in which the drug is released gradually and steadily from the gum base. Medicated chewing gum should be chewed for a certain period of time to deliver the dose, and then discarded.

MEDICAL GUM HISTORY

As far back as a thousand years ago, the Mayan Indians chewed the tree resin from a sapodilla tree in order to clean their teeth and freshen their breath [4].

MECHANISM OF RELEASE OF DRUGS

The medicine releases after mixing with saliva when the CG is chewed for a specified amount of time. As an outcome, the medication in the chewing gum releases the medication, which can then be absorbed either through the oral mucosa, which has a rich blood supply, or by swallowing and passing through the stomach for gastrointestinal absorption before being spit out.

Therefore, there are two methods for a drug of choice to enter the bloodstream first pass liver metabolism and absorption through to the buccal barrier, which blocks gastrointestinal metabolism [5].

Corresponding Author :- Tanam. Srikala Email:- ksri83682@gmail.com

TRENDS IN THE FUTURE

An oral contraceptive that can be chewed will be available in the near future: In the coming year, women will have another option for birth control - chewable pills. An FDA-approved chewable birth control drug will be marketed by Warner Chilcott Inc. next spring in spearmint flavor [6].

MATERIALS

Hydroxyzine Hydrochloride

- Administered orally or via intramuscular injection.
- When given orally, hydroxyzine is rapidly absorbed from the gastrointestinal tract. The effect of hydroxyzine is notable in 30 minutes.
- Higher concentrations are found in the skin than in the plasma.
- The T_{max} of hydroxyzine is about 2.0 hours in both adults and children [7, 8].

Excipient profile of MCG

Sorbitol, Sucralose, Mint (Peppermint oil), Aerosil, Magnesium stearate, Talc, Alizarin Green, Pharmagum.

Methodology

I. PRE-FORMULATION STUDIES

A. 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 melting point of the drug was determined by capillary
- fusion method. A capillary was sealed at one end filled with a small amount of drug and the capillary was kept inverted i.e. sealed end downwards into the melting point apparatus. The temperature at which the drug melted was noted down using the thermometer provided [9].

Spectrometric Identification of Drug by using UV spectroscopy

10 mg of Drug sample was dissolved in 25 ml of absolute alcohol (ethanol) and volume made up to 50 ml with phosphate buffer solution (PBS) pH 7.4. From this stock solution take 0.5 ml was taken into a 10 ml volumetric flask and made up the volume to 10 ml with PBS pH 7.4. These solutions contain 10µg of drug per ml of PBS pH 7.4 [10µg/ml]. Finally, sample [10µg/ml] was scanned in the range of 200 – 400 nm using UV - spectroscopy to determine the λ max [10].

B. Pre-compression Characteristics

- **Bulk Density**

It is the ratio of total mass of the powder to the bulk volume of powder. It was measured by pouring the weighed powder in to measuring cylinder and the volume was noted. It is expressed in gm/ml and givenby,

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

- **Tapped density**

It is the ratio of total mass of the powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by,

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

- **Compressibility index**

The compressibility index of the powder blend was determined by carr's compressibility index. It is simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's index is as below,

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

- **Hausner's ratio**

It is calculated from bulk density and tap density,

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

- **Angle of repose**

The frictional forces in loose powder can be measured by the angle of repose θ. The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the formed powder heap.

- **Loss on drying**

Loss on drying was measured in halogen moisture balance instrument for 4 minute at 105°C.

C. Compatibility studies for drugs and excipients

The Drug - Excipient interaction studies were carried out employing IR spectroscopic techniques. The sample [Pure Drug and Drug + Excipients] was dispersed in KBr and compressed into pellets. The pellets were placed in the light path and the spectrum was recorded in the wavenumber region of 4000-400 cm-1. IR spectra of Drug with and without polymers [Eudragit RL 100 & Ethyl cellulose] were obtained.

D. Formulation Development

Conventional method

Formulating a new chewing gum involves exploring the possibilities of utilizing available manufacturing technologies. The conventional methods of manufacturing medicated chewing gums include a variety of techniques not just melting, blending, hot melt extrusion, drying, and packaging.

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 techniques of producing and optimizing the product release behavior have yet to be fully explored and explored in terms of the techniques of manufacturing and optimizing the release behavior. There are a number of research activities underway in order to extend this platform so that it can be used to deliver drugs more efficiently and economically

All the ingredients were weighed accurately as per the formula; weighed ingredients were passed through sieve no. 16 for reduce the particle size and kept a side. First the flavor and aerosil were mixed and thoroughly and kept a side. The drug, pharmagum M, sorbitol, and sucralose were mixed.

Finally to this the weighed quantities of Magnesium stearate were added. The mixture was then re-granulated by passing through sieve no 30. The granules were weighed and then compressed using a 14mm punch in rotary tablet punching machine. In the present study six sets of formulations were prepared and studied.

E. Characterization of prepared formulation

- **Friability Test**

It is usually measured by the use of them 'friabilator'. 10 tablets were randomly selected, weighed and were tested using the Veego friabilator

$$\text{Friability} = \frac{\text{Winitial} - \text{W final}}{\text{W initial}} \text{X } 100$$

- **Weight Variation**

The weight variation test of the chewing gum was done as per the guidelines of USP 20. Chewing gum was randomly selected, weighed and weight was noted and the mean weight was calculated. Percentage deviation of each chewing gum from the mean was calculated.

- **Hardness test**

The Monsanto hardness tester measures the force required to break the chewing gum.

- **Estimation of drug content**

Chewing gums unlike tablets cannot be assayed by the conventional method that is by crushing the tablet and weighing an accurate amount of medicament and estimating its content. For estimation of the drug content in chewing gums and for the study of drug release process from chewing gums a new apparatus (Erweka's DRT 6 Chewing apparatus) has been designed which mimics the natural chewing actions [10].

Procedure:

The test cell was filled with 50ml of simulated salivary fluid (SSF). The chewing gum was placed in the equipment and the instrument was operated for a period of 30 minute at a chewing frequency of 56 strokes/ min, to ensure total release of the drug from the formulation in the simulated salivary fluid. From the dissolution medium 5 ml was withdrawn and volume was made up to 100ml with SSF and the absorbance of the resulting solution was read at 232nm. The amount of drug present in the formulation is calculated.

***In vitro* drug release**

The test cell of the apparatus was filled with 50ml of SSF and the chewing gum was placed in the apparatus. The apparatus was operated at a chewing frequency of 50 strokes / min. 5ml of the SSF from the test cell was withdrawn at regular intervals of 5, 10, 15, 20, 25 and 30 min 5ml of fresh SSF was replaced back in the test at every withdrawal of the sample [11]. The volume withdrawn was made up to 100ml using SSF and absorbance of the resulting solution was read at 232nm, process parameter show in table: 2

Table 1: Formula of MCG preparations.

Ingredients	Formulation (1000 mg chewing gum) Code					
	F1	F2	F3	F4	F5	F6
Hydroxyzine Hydrochloride	5	5	5	5	5	5
Pharmagum M	300	300	330	320	310	325
Sucralose	625	615	575	630	625	625
Sorbitol	15	15	15	15	15	15
Aerosil	10	19.75	25	0.05	0.05	0.05
Magnesium stearate	0.25	0.25	1	0.50	0.75	1
Talc	30	30	34	20	30	15
Mint flavor & Alizarin green colour	15	15	15	10	15	15

Table 2: Dissolution process parameters

Dissolution medium	SSF Fluid at pH6.6
Temperature	37±0.5^{o}C
Chewing frequency	50 stroke/min
Volume withdrawn and replaced	2ml every 2 min
λ max	232 min

Blank solution	Simulated salivary fluid
Volume	50ml

Table 3: Organoleptic characteristics of Drug.

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

Figure 1: Buccal Mucosa of Human- A Cross section.

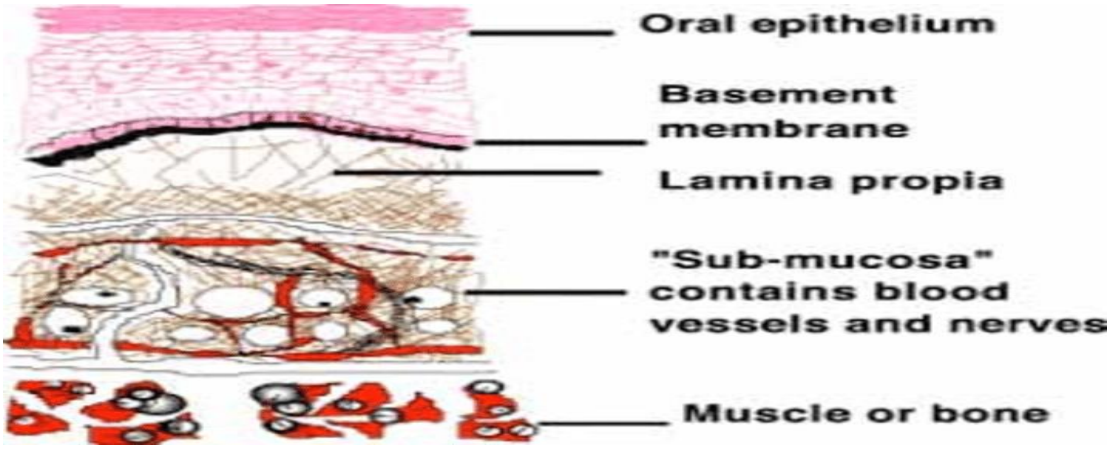


Figure 2: UV Spectrum of Hydroxyzine hydrochloride.

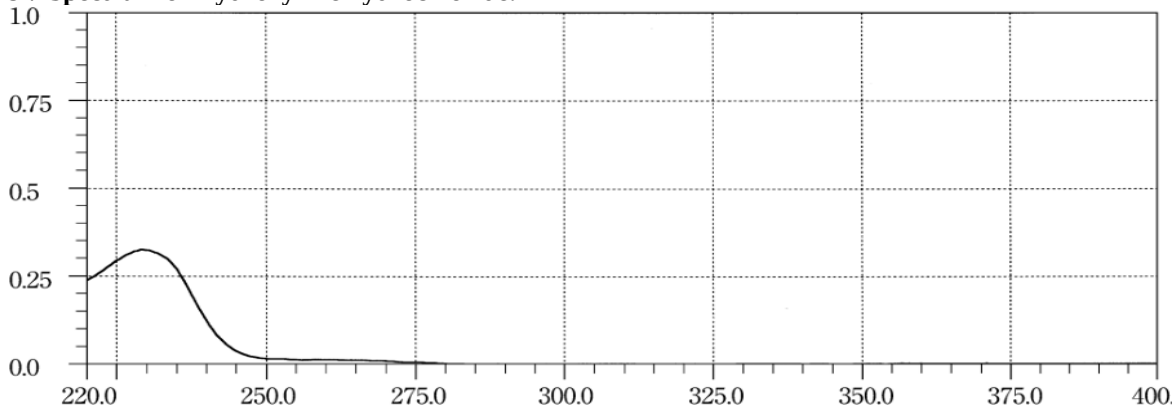


Figure 3: Bulk density of MCG

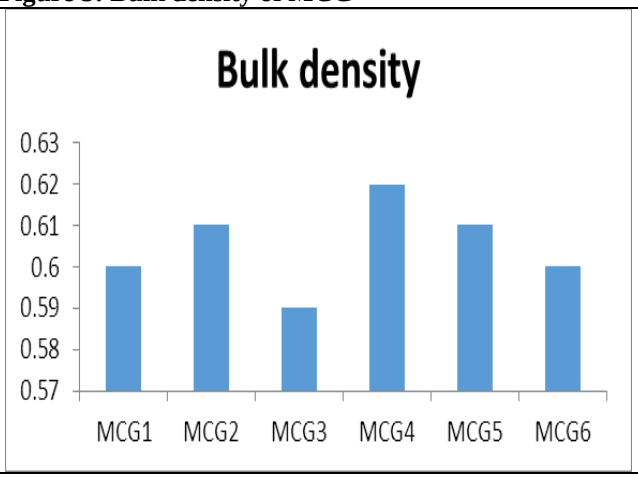


Fig: 4 Tapped density of MCG

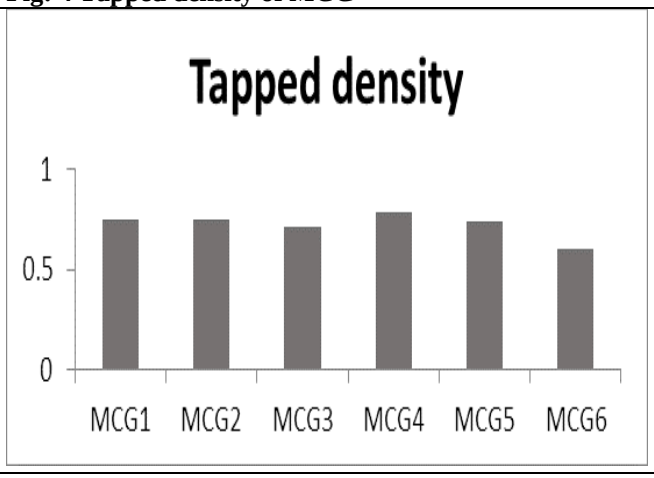


Figure 5: Compressibility index of MCG

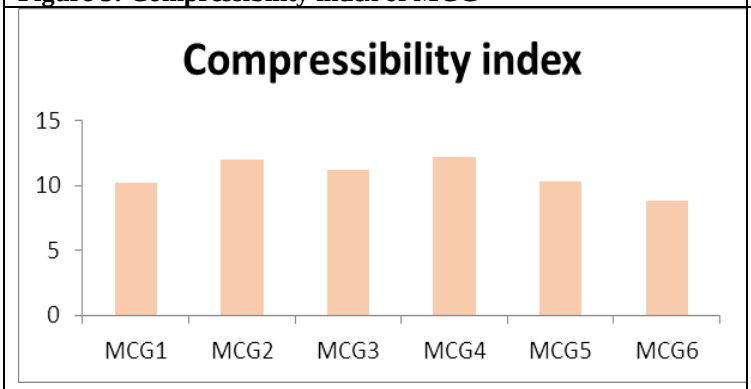


Figure 6: Hausner's ratio of MCG

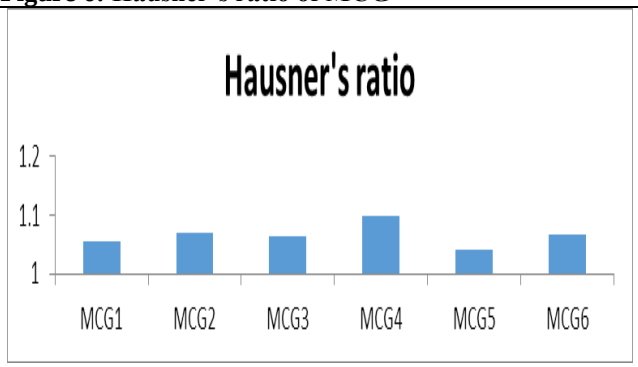


Figure 7: Angle of repose of MCG

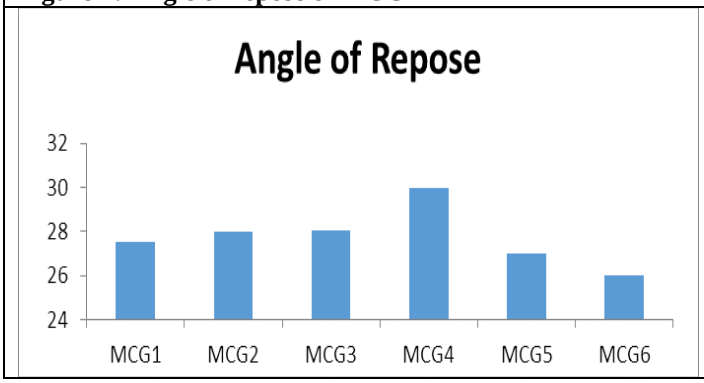


Figure 8: Loss on drying

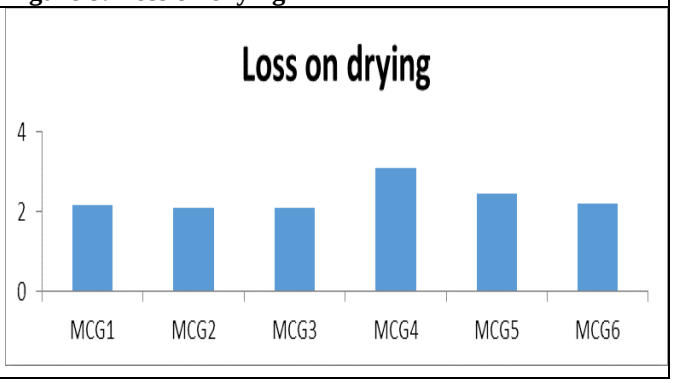


Figure 9: IR Spectrum of Pure Drug.

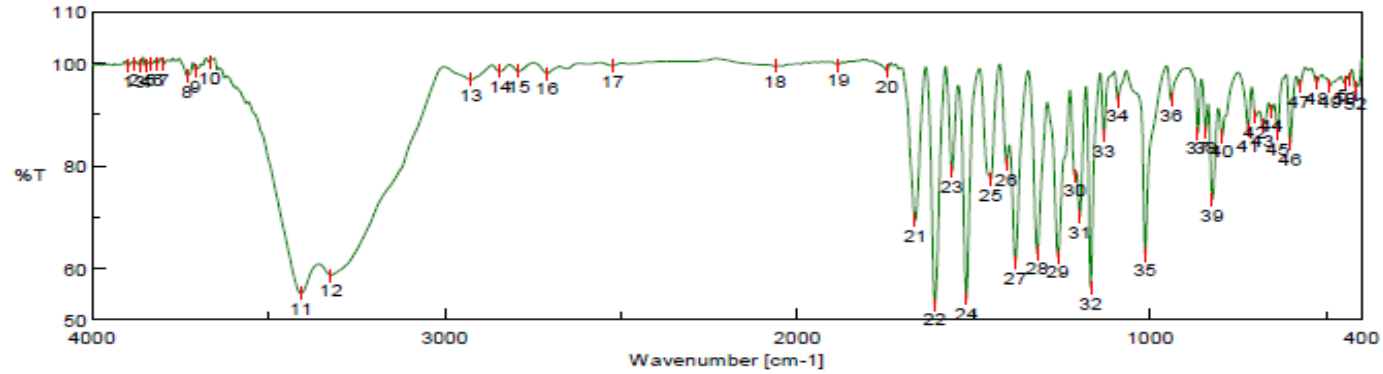


Figure 10: IR Spectrums of Pure Drug and Pharmagum M

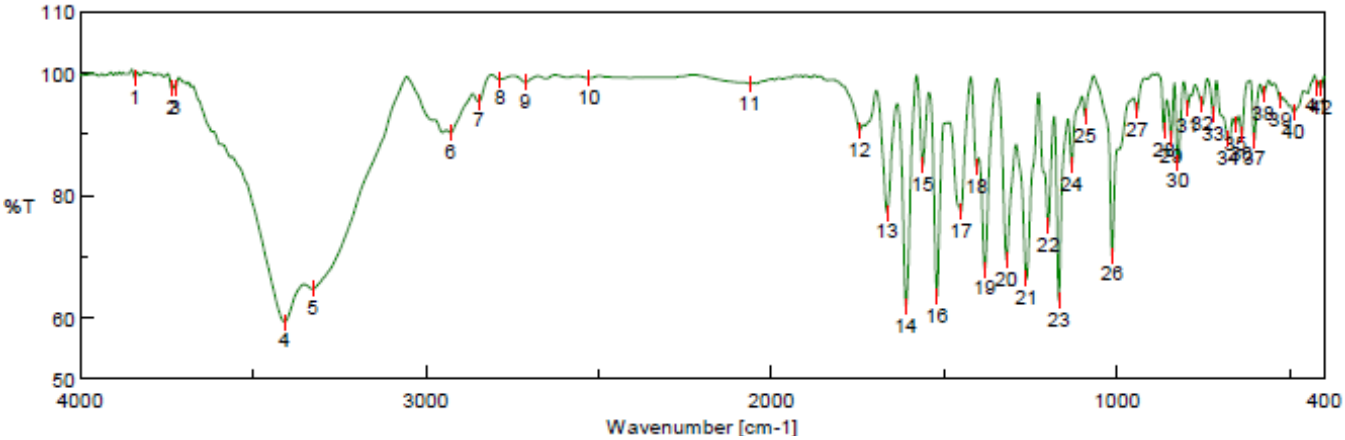


Figure 11: Friability study of MCG

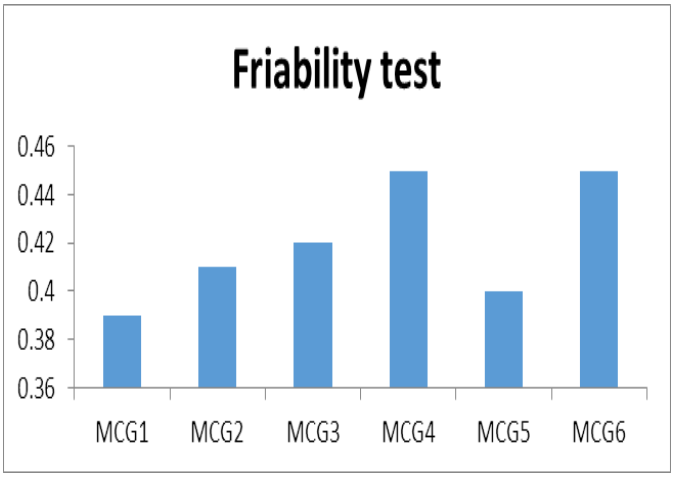


Figure 12: Weight variation test of MCG

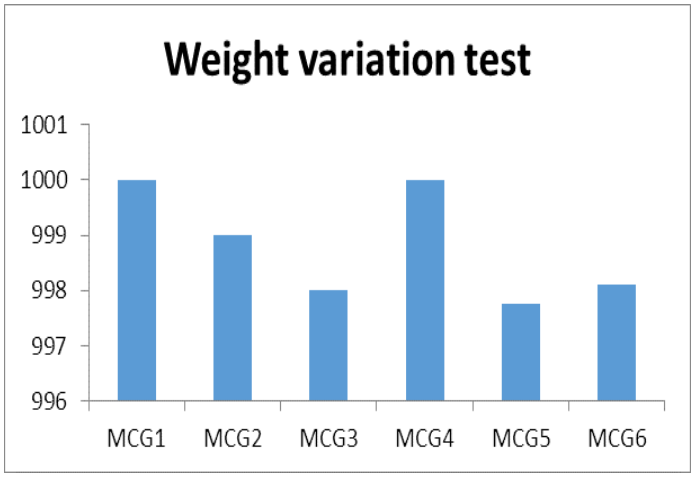


Figure 13: Hardness test of MCG

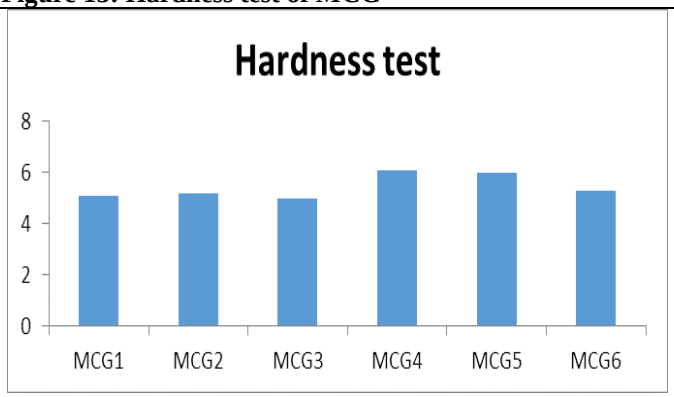


Figure 14: Drug content of MCG

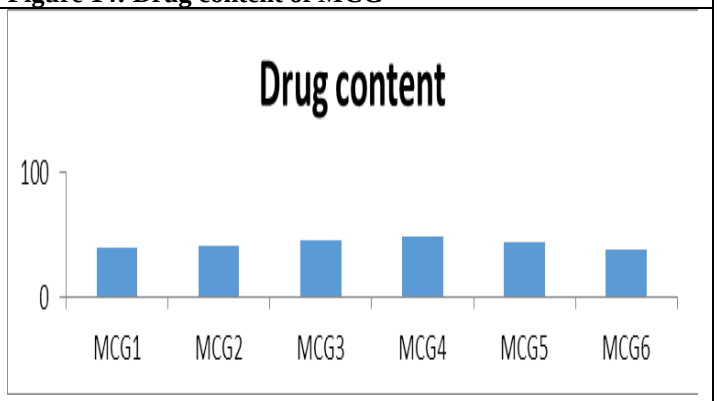
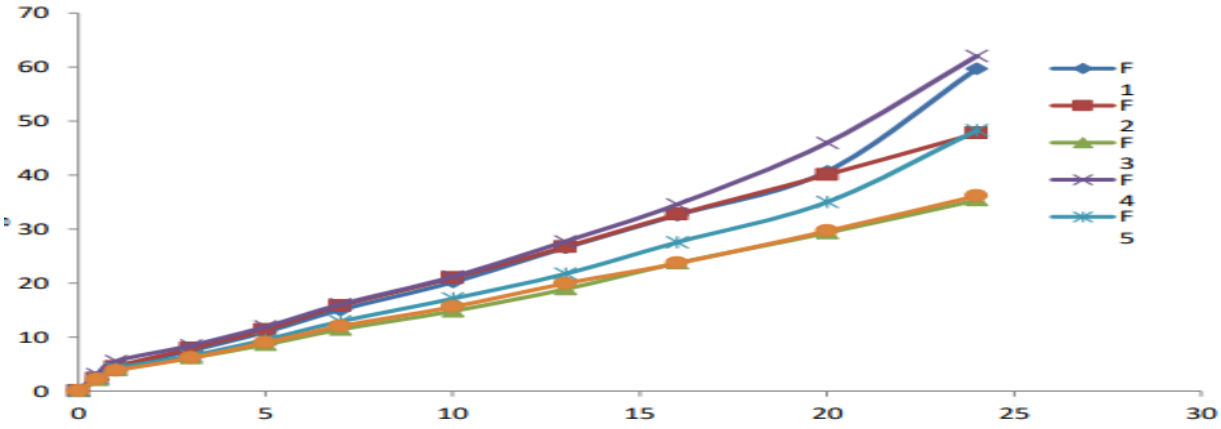


Figure 15: Dissolution profile of F1 to F6 of MCG



RESULTS

- **Identification of Drug**

Determination of organoleptic characteristics of Hydroxyzine hydrochloride:

The colour, odour and appearance of drug were characterized and recorded; the results were shown in the table: 3.

Determination of Melting Point

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

- **Spectrometric Identification of Drug by using UV spectroscopy**

The absorption maxima **(**λ max) were determined to be at 232nm. The UV spectrum was shown in below figure: 2.

A. Pre-compression Characteristics

- **Bulk density**
- **Compatibility studies for drugs and excipients**

The drug excipient interaction studies were carried out employing FT-IR Spectroscopic technique. The characteristic peaks observed in the FT-IR spectrum of physical mixture of hydroxyzine hydrochloride and polymers showed no shift and no disappearance of characteristic peaks of drug. This suggests that there was no interaction between hydroxyzine hydrochloride and polymer. The IR spectrum of Pure Drug and Physical mixtures was shown in Figure and Characteristics peaks are summarized in table.

The comparison between the peaks of two graphs shows that the characteristics peaks of Hydroxyzine hydrochloride (Reference) was found to be similar to the given drug sample, which shows that the drug is hydroxyzine hydrochloride.

I. Formulation Development

The six different formulations [F1-F6] of Hydroxyzine hydrochloride was formulated by using polymer and its different concentration along with different plasticizers by simple conventional method. The prepared formulations are then evaluated for various parameters like friability test, weight variation, hardness test, drug content estimation, *in vitro* drug release and chewing gum consistency.

II. Characterization of prepared formulation

The prepared formulations are then evaluated for various parameters like friability test, weight variation, hardness test, drug content estimation, *in vitro* drug release and chewing gum consistency. The results are mentioned in the table.

- **In vitro drug release**

The chewing frequency of 50 strokes/ minute was applied. Formulation MCG4 showed highest drug release of 95.88% at the end of 30 minutes and formulation MCG6 showed lowest drug release of 38.75% at the end of 30 minutes.

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. It also prevents motion sickness by reducing excitability of neurons in the motion and balance center (vestibular region) of the brain.

The results were compared in results the formulations MCG3 and MCG5 showed good drug release rate but these formulations did not show sufficient chewing gum like consistency. Remaining formulation MCG1, 2, and 6 have low drug release and not proper chewing gum like consistency. Mcg 6 has sticking problem due to excess amount of gum.

It is seen that as the concentration of the gum base and magnesium stearate maintained in proper amount than drug release is highest. Thus it can be said that with varying the concentration of gum base and magnesium stearate in the formulation, the drug release can be controlled. Thus we have successfully formulated medicated chewing gums containing hydroxyzine hydrochloride.

As the concentration of gum increases in excess amount the drug release from the formulation decreases i.e. we can sustain the release of drug. But as we increase the gum concentration it creates problem at the time of compression. Here the gum will stick to the punches and dies. So the formulations MCG 6 cannot be prepared in large batch size.

The study showed that modifying parameter like gum base and soya powder concentration, the drug release from the chewing gum can be adjusted to the desired rate and at the same time mask the slight bitter taste of drugs.

CONCLUSION

Medicated chewing gums containing hydroxyzine hydrochloride were successfully formulated using Pharmagum M as the gum base and Magnesium stearate to obtain cost effective formulation and for better patient compliance. Among all 6 formulations, MCG4 showed better pre-compression characters, post-compression characters, drug content, *in vitro* drug release and good stability. So, MCG 4 was selected as optimized batch. From this study it can be concluded that it is possible to design medicated chewing gum containing hydroxyzine hydrochloride, mainly for the treatment of nausea and vomiting related conditions, where efficacy and patient compliance are of prime importance.

REFERENCES

1. Flora Ferreira Duarte de Oliveira, Livia Rodrigues de Menezes, Maria Inês Bruno Tavares. Film-Forming Systems in Topically Administered Pharmaceutical Formulations. *Materials Sciences and Applications.* August 14, 11, 2020, 576-590.
2. Shojaei AH. Buccal mucosa as a route for systemic drug delivery: A review. *J Pharm Pharm Sci*, 1(1), 1998, 15-30.
3. Surana AS. Chewing gum: A friendly oral mucosal drug delivery system. *Int J Pharm Sci Rev Res* 4(2), 2010, 68-71.
4. Munksgaard EC, Nolte J, Kristensen K, *et al*. Adherence of chewing gum to dental restorative materials. *Am J Dent* 1995, 8(3), 137-9.

5. Nilima T, Karishma P, *et al.* A review on medicated chewing gum as a novel drug delivery system. *Journal of Pharmacy Research* 4(3), 2011, 848-851.
6. Malke SS, Shidhye SS, Desai AS, Kadam VJ, *et al.* Medicated Chewing gum-A novel option. *Indian drugs*. 43(3), 2006 191-198.
7. VISTARIL (hydroxyzine pamoate) Capsules and Oral Suspension" (PDF). pfizer.com. 2006. Archived from the original (PDF) on 3 July 2007. Retrieved 7 March 2007. The extent of renal excretion of VISTARIL has not been determined. *United States Food & Drug Administration*, 2004, 2.
8. Shidhaye supriya shrihari. Sustained release nail lacquer formulation containing combination of luliconazole and methyl salicylate for the treatment of onychomycosis. *Int. J. Drug. Dev. Res.* 13(3), 2021, 6043.
9. Cherukuri G, Subraman R, Krishnayya B, *et al*. Tabletted chewing gum composition and method of preparation. *United States Patent*, 19, 4753805.
10. Gmunder CB, Li W, Ream R, *et al*. Sildenafil chewing gum formulation and methods of using the same US6592850B2;