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FORMULATION AND EVALUATION OF LAYERED CHEWING GUM TABLET CONTAINING DOXYLAMINE SUCCINATE

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Abstract: People present in the society especially youngsters chew various kind of gum base which are available in different flavors and different brand. Medicated chewing gum is nothing but a gum base which contain API for treatment for certain type of disease. Due to chewing result in drug release from the chewing which get mix[1] into the saliva and get penetrate into the mucosa hence increase bioavailability of drug as the release of drug by pass hepatic metabolism and also prevented from gastric degradation. As the buccal cavity is highly vascularized so, concentration of drug achieved in systemic circulation occur frequently. The release of drug from the chewing gum is directly proportional to mastication and time of chewing gum placed in mouth[2].In contrast, medication produced from medicated chewing gum that is not absorbed via the membrane of the oral cavity will be ingested and arrive in the stomach in a very fine dispersed form, making it easily available for gastrointestinal absorption with a resulting rapid beginning of action. Dose given in medicated chewing gum is less as compared to conventional dosage form.

Key Words: Medicated Chewing gum, Polyvinyl Pyrrolidine (PVP), Eudragit EPO, Franz Diffusion Cell, Magnetic Stirrer, punching machine

Introduction: The most severe kind of nausea and vomiting during pregnancy, known as hyperemesis gravidarum (HG), is characterized by continuous nausea and vomiting coupled with weight loss (>5% of pre-pregnancy weight) and ketosis. Volume loss, electrolyte and acid-base imbalances, nutritional deficits, and even mortality might result from this illness. In 0.3–2% of pregnancies, severe hyperemesis necessitating hospitalization occurs. The complexity of traditional formulations to release the medicine over long periods of time is the basic attraction of formulating layered chewing gum as dosage forms. Marketed formulated available consists of delayed release tablets which release the drug over a period of time with delayed onset. The present study aims at formulating Doxylamine succinate chewing gum to improve the onset of action which improves patient compliance. The chewing gum base is sandwiched between two anti-adherent layers so that tablet compression machine can be used to formulate the layered chewing gum.

Materials and Methods

Materials

Doxylamine succinate was purchased by Yarrow chemicals, India, beeswax, PVP and Eudragit EPO was purchased by Loba Chemical Pvt limited, Mumbai, India. All the solvents and reagents used were of analytical grade.

Methods:

A) Pre-Formulations Studies

I)Standard plot of Doxylamine Succinate in water:

The analysis was carried out using UV spectrophotometer. The λ maximum was observed in water. The absorbance values of these solutions were read at 260 nm, in UV spectrophotometer against Water as blank. Standard plot of Doxylamine Succinate in water is as shown in Figure 2

II) FTIR (Fourier Transform Infrared Spectroscopic) Studies: FTIR of Doxylamine Succinate used to investigate the drug's structural and molecular makeup, as well as its properties that affect how it works. FTIR studies were also performed for excipients, physical mixture and formulation to rule out possibilities of drug-excipient interactions.

Overlay FT-IR spectrums are Shown in Figure 2

III)Quantitative Determination (Solubility Analysis):

It was performed by taking 2–5 neat and clean ampoules .150 mg/ml drug powder was added and excess solvent (distilled water) was added into the breaker. At last, the absorbances was measured in the UV spectrophotometer at 260nm. Solubility analysis of Drug, PVP, Eudragit along with their combinations were performed for further evaluation.

B) FORMULATION OF MEDICATED CHEWING GUM

Table 1: Formulation Table

S. No.	Ingredients	Quantity
1	Doxylamine Succinate	0.020 g
2	Ascorbic acid	0.2 g
3	Beeswax	1.0 g
4	Eudragit/PVP	0.1 g
5	Dextrose	0.7 g
6	Peppermint oil	0.5 ml
7	PEG-400	0.8 ml
8	Calcium carbonate	0.5 g

Layered Chewing Gum Tablet was formulated into two steps. The first step is the preparation of chewing gum base containing drug and second step is the preparation of anti-adherent layers

STEP-1) Method of Preparation of Chewing gum Base containing Drug: The direct compression mold method was used to create MCGs. Each ingredient was precisely and separately weighed in this technique. In a mortar, all of these were thoroughly combined in descending order of their weights. Following thorough mixing, components were smoothly mashed in a mortar and pestle. The mixture was compressed into the desired molds and presses after mixing and grinding to create medicated chewing gum[3], as shown in Figure 4 Formulated chewing gums were weighed and neatly wrapped after being removed from the mold.

STEP-2) Method of preparation of anti-adherent layer: The trituration method was used to create layered chewing gum. Each ingredient was precisely and separately weighed in this technique. In a mortar, all of the ingredients—dextrose(1gm), Talc (2 gm), magnesium stearate (2 gm) and colloidal silicon dioxide (0.8 gm)—were thoroughly combined in descending order of their weights. Following thorough mixing, components were smoothly mashed in a mortar and pestle. After the preparation of Gum base and layer, chewing base was incorporated between the two layer as shown in the Figure 4.

C) Optimization

Experimental Designing: Here, a commercially available software program was used (Design Expert, Version 11, Stat-Ease Inc, and Minneapolis, MN). The experimental design chosen was response surface 2- level factorial; 4 formulations were formulated. Run order was kept in the randomize mode to protect against the effects of time related variables and also to satisfy the statistical requirement of independent variables.

The factors considered were:

(1) Amount of PVP

(2) Amount of Eudragit.

Factor A- PVP Concentration: PVP concentration was varied to study the effect on taste masking, effect on hardness and percent drug release from the formulation and also prevent the Mannich reaction between Doxylamine succinate and dextrose Levels of factor A are shown as below

Table 2.1: Levels of Factor A- PVP Concentration.

Level of factor (A)	*Coded value*	*Concentration(g)*
Low	-1	4.4
High	1	4.5

Factor B- Eudragit Concentration: Eudragit concentration was varied to study the effect on hardness and percent drug release from the formulation

Levels of factor B are shown in below

Table 2.2: Levels of Factor B- Eudragit Concentration.

Level of factor (B)	*Coded value*	*Concentration(g)*
Low	-1	0.1
High	1	0.2

The formula of Layered Chewing Gum Tablet Containing Doxylamine Succinate was based on 2^2 factorial designs where each of the two factors were considered at two levels. Thus, as shown in below table total 4 batches were prepared.

Table 2.3: Design matrix for Experimentation:

Batches / Ingredients	**MCG 1**	**MCG 2**	**MCG 3**	**MCG 4**
Drug (mg)	20	20	20	20
PVP (g)	4.5	4.4	4.5	4.4
Eudragit (g)	0.1	0.2	0.2	0.1

D) EVALUATION

1) Friability Test: Layered chewing gum tablets have a propensity to cap while being handled and transported, which has an impact on the quality, appearance, medication content, and coating specifications; as a result, a friability test is conducted. The device employed is a Roche friabilator, which comprises of a revolving disc with a 12-inch diameter and a 100-rpm rotational speed. The evaluation was conducted on 20 layered chewing gum tablets which were placed on the disc and rotated these for 100 rotations. As per the literature if, Percentage of Friability is less than one then the formulation pass the test.

From the Experiment the Precent Friability is found to be 0.04% i-e within the range Hence, the given formulation passes the test

2) Weight variation test: The weight variation test would provide a reliable way to assess the uniformity of drug distribution in terms of content. When tablets contain 50 mg or more of the drug substance or when the drug substance accounts for 50% or more (by weight) of the dosage form unit, the weight variation test is applicable[4].

Average weight of 20formulation= 401.25mg. The weight variation test's value is given as a percentage.

The formula is as follows:

Weight Variation (%) = (Weight of Single Formulation/Mean weight of 20 formulation) *100

In order to pass the weight variation test of given formulation. As per the Literature if Average weight of the formulation is more than 300mg then formulation should not be differed from the mean weight by more than 7.5%[7]

Hence, the given formulation passes the Weight variation Test as it was found within the range

3)Moisture content: The moisture content of a tablet was determined by using a desiccator, in which a sealed container contains a desiccant, such as silica gel or anhydrous calcium chloride, to absorb moisture from the sample[5].

The moisture content of the tablet was calculated using the following formula:

Moisture content = [(W1 - W2) / W1] x 100

W1=the initial weight of the tablet and

W2=the weight of the tablet after drying in the desiccator.

Note: that it is important to ensure that the desiccator should be properly sealed and that the desiccant is fresh and has not already absorbed moisture from the air.

After performing moisture content test no difference in the formulation weight was observed.

4) In vitro drug release studies: A medicated Chewing gum was dissolved in 10ml of distilled then that solution of a medicated Chewing gum was submerged in a 40ml of Phosphate buffer solution with a PH of 6.8(buccal cavity) then kept it in on magnetic stirrer and subjected to stirring. After every 5 minutes, 2ml of solution was withdrawn and replaced with 2ml of buffer solution The volume of withdrawn solution(2ml) was adjusted using distilled water up to 25ml.sample were taken out at regular intervals of 5,10,15,20,25,30 minutes. After the process was completed, a maximum wavelength of 260nm was used to examine all the of the gathered samples using UV Spectrophotometry. Only concentrations of PVP and Eudragit were changed in all four formulations and other ingredients concentration remain same which is mentioned in formulation table.

Invitro release of four different formulations having varied concentration of PVP and Eudragit are shown in figure 8

5) Hardness Testing: All Medicated Chewing gum formulations were evaluated for hardness using a Pfizer type hardness tester because there is no established procedure for doing so. Hardess testing of four formulations according to factorial design shown in table 6.

6)Ex-vivo buccal permeation Study: Using a Franz diffusion cell, as shown in Figure 9, this study calculates the overall quantity of drug penetration across the membrane. The experiment was performed by taking goat buccal mucosa. The membrane was cleaned and positioned between the salivary chamber (donor) and a blood chamber (receiver) of the Franz diffusion cell. The Drug concentration obtained from Ex-Vivo studies are given in Figure10.

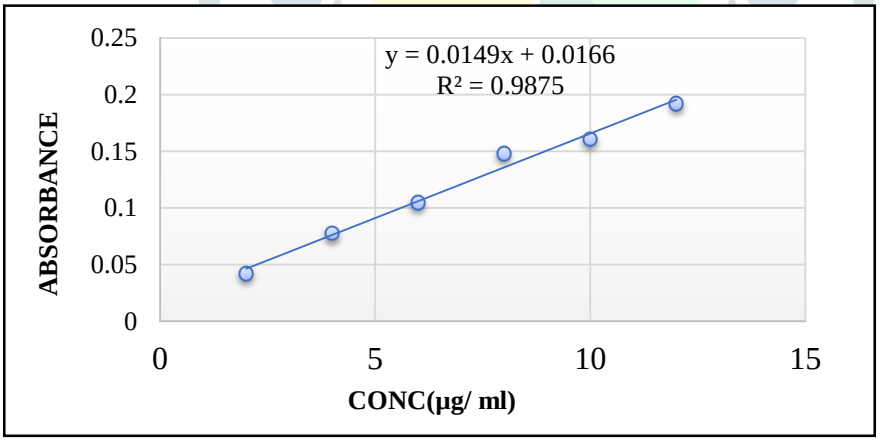
E) RESULTS AND DISCUSSIONS

I) Standard plot of Doxylamine Succinate

Table 3: Standard plot of Doxylamine Succinate

CONC (micro gram/ml)	ABS (nm)
2	0.042
4	0.0777
6	0.105
8	0.1477
10	0.1608
12	0.1922

Figure 1: Standard plot of Doxylamine Succinate in water



The standard plots were constructed for Doxylamine Succinate in water. The r^2 value [regression] would indicate the suitability and linearity of the treatment. r^2 value for standard plot for water was 0.9875 which indicates a good linear relationship.

II) FT-IR Spectrum for drug-excipient interactions

Figure 2 displays the overlay spectrum of drug, excipient and formulation. FT-IR spectrums shows that no possible degradation of drug peak in physical mixture and formulation spectrums which complies with accepted functional group frequencies.

Table 4:IR frequencies of Doxylamine Succinate

Functional group	Characteristic Wavenumber (cm-1)	Doxylamine succinate observed Wavenumber (cm-1)
C6H5	650-600	626.87
C-CH3 bending	1458-1380	1469.76
C-O-C	1300-1000	1388.75
C=N	1650-1550	1641.42

Figure 2: Overlay FT-IR Spectrum of [A]Doxylamine Succinate, [B]Eudragit EPO, [C]Physical mixture and [D]Formulation

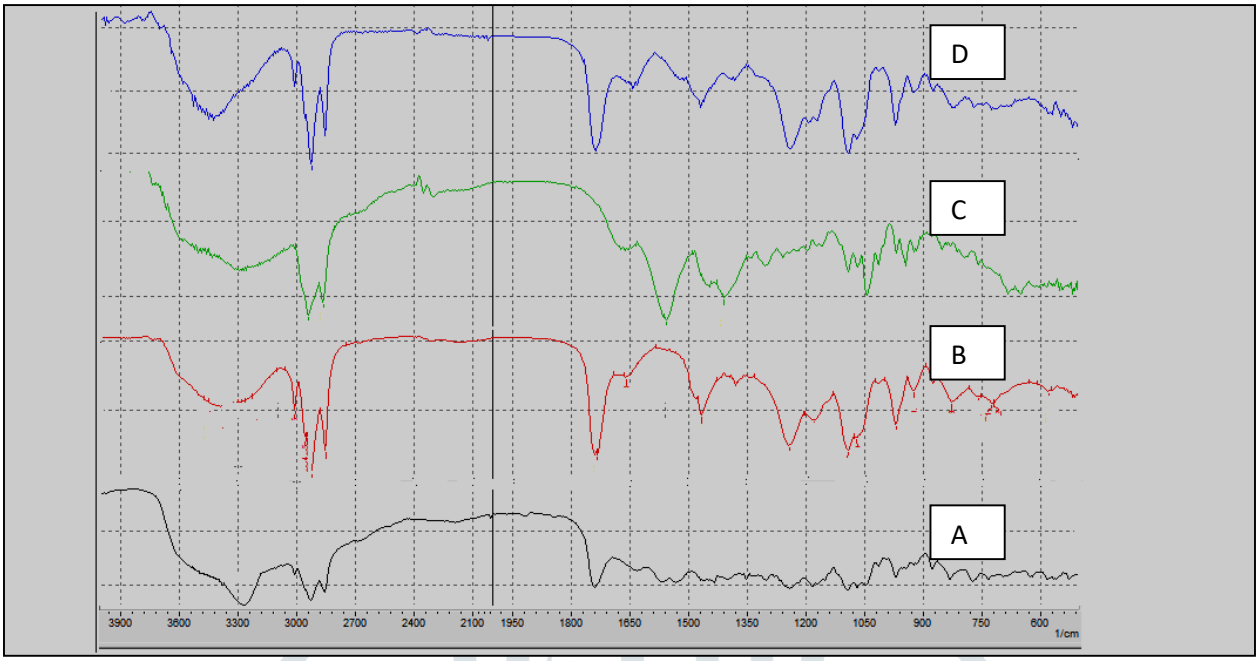


Figure 3: Steps for the Formulation of Layered Chewing Gum Tablet

Step-1) Formulation Layer

Step-2) Chewing Gum Formulation

Figure 4: Steps for the Incorporation Of the and layer

Chewing base

Direct compression

Step-1(Only Layer)

Step-2 (Chewing Gum base with Drug)

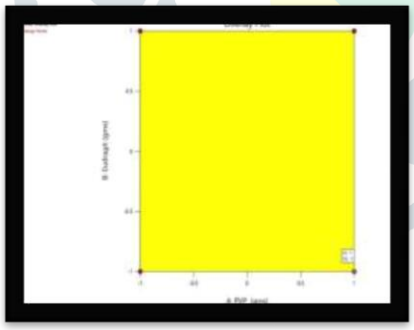
Step-3 (Layer on above Chewing gum base)

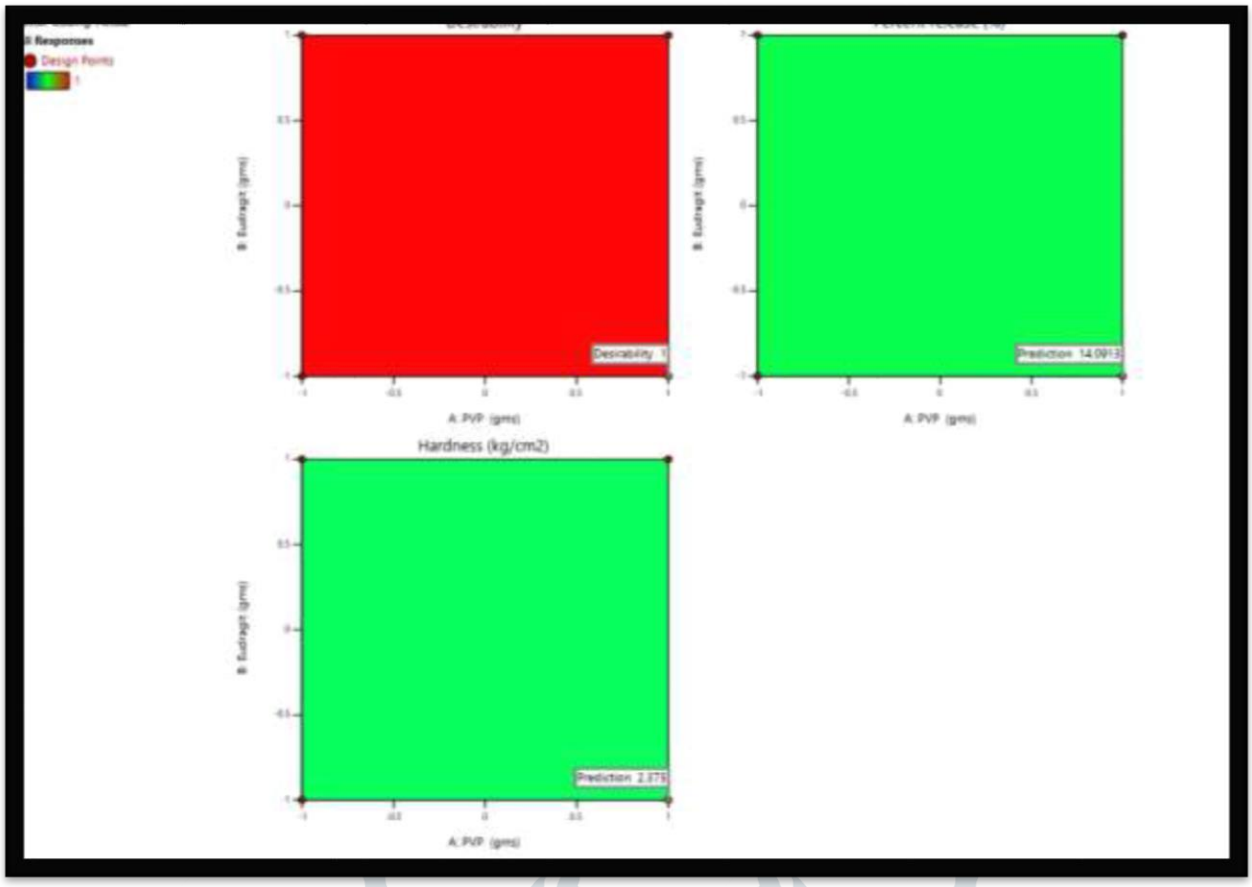
LAYERED CHEWING GUM TABLET CONTAINING DOXYLAMINE SUCCINATE

Figure 5: Formulation with PVP and Eudragit

After placing the chewing Gum Formulation in room temperature for one day it turns brownish color as shown in above Figure. because the Probable Mannich reaction between the Doxylamine succinate and Dextrose which destabilize the Formulation. Hence, in order to prevent the reaction between the Drug and Dextrose we replace the polymer i-e Eudragit with PVP (Poly Vinyl Pyrrolidone)

Figure 7: Experimental Designing/ Factorial design





Formulation of Layered Chewing gum tablet Containing Doxylamine Succinate was designed according to 22 Full factorial design by using two independent variable i-e Concentration PVP (Polyvinyl Pyrrolidone) and Eudragit at two level Low (-1) and High (+1) as given in tableno.5.5.1 and the dependent parameter selected was Invitro drug release(Y1) and Hardness(Y2) of the formulations. The Software design Expert from State Ease was used to determine the impact of changes in independent variable on dependent variable (Y1 and Y2). The desirability and overlay plot were obtained of the best optimized formulation along with predicted values for Y1and Y2.

The Desirability of optimized formulation was found to be (1) as shown in Fig. 6.11 (b)The optimized chewing gum were prepared according to the composition which were obtained in overlay plot as shown in the Fig. 6.11 (a) and these are evaluated at two dependent parameters Hardness and invitro release which are found to be and 14.0913 % and 2.375 kg/cm2 release Respectively[6].

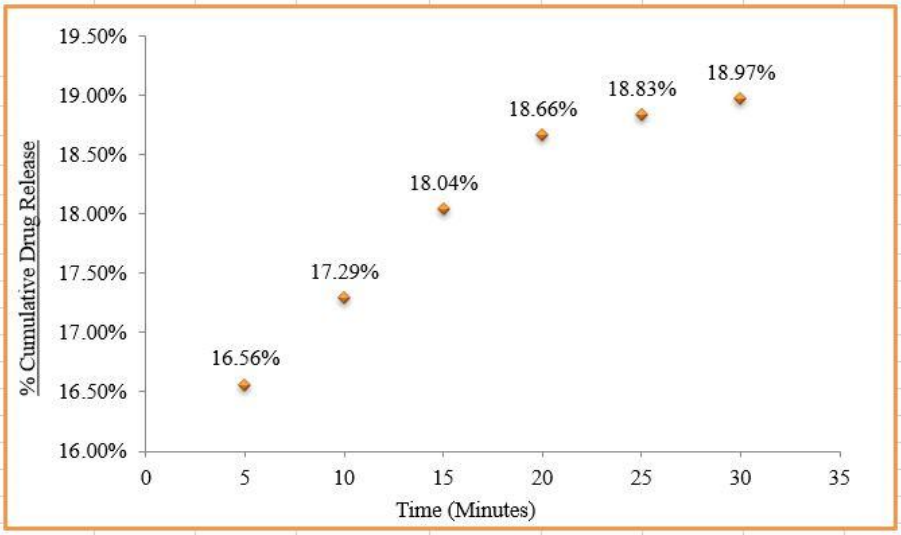
Table 5: 2^2Factorial Design

Independent Variables	Optimum Values		Dependent Variables	Observed Value	Predicted Value	Difference
	(Code)	(mg)				
A	+1	4.5	Y1(% release)	25.17%	14.0913%	11.077%
B	-1	0.1	Y2(Kg/cm2)	3.9 kg/cm2	2.375 kg/cm2	1.6 kg/cm2

According to 2^2 Full factorial design Four Formulation of Different Concentration of PVP (Polyvinyl Pyrrolidone) and Eudragit. Invitro drug release and Hardness testing was evaluated of these Four Formulation

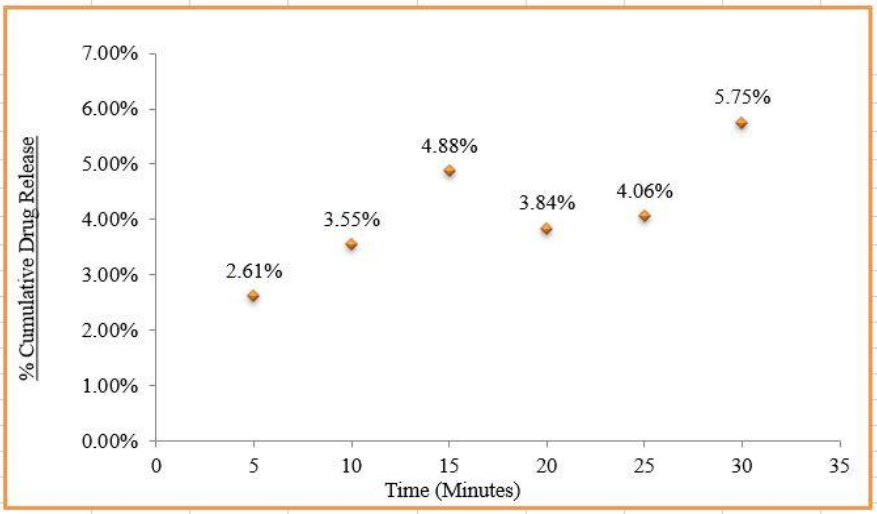
Figure 8: In vitro drug release studies.

I) PVP:4.5g, Eudragit 0.2g



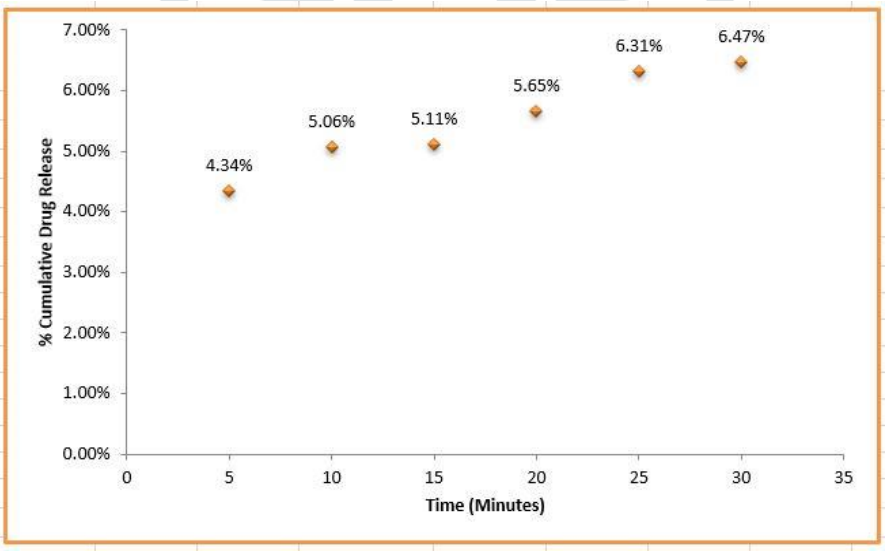
Percent release of above formulation is found to be 18.97%

II) PVP:4.4, Eudragit:0.2



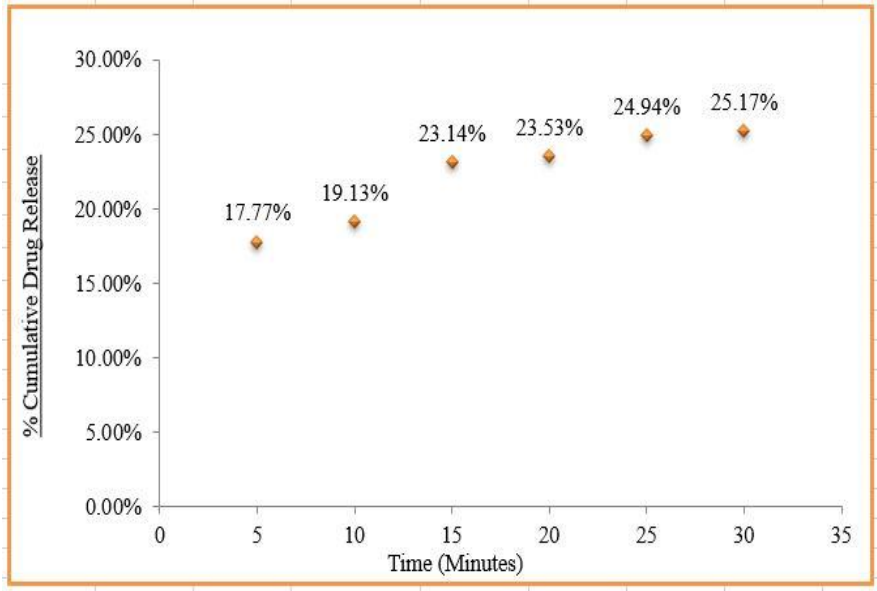
Percent release of above formulation is found to be 5.75%

III) PVP:4.4g, Eudragit 0.1



Percent release of above formulation is found to be 6.47%

IV)PVP:4.5g, Eudragit:0.1g



Percent release of above formulation is found to be 25.17%

From the above Four Formulation the Optimized formulation is with (PVP:4.5g, Eudragit:0.1g) because it shows maximum % drug release i-e 25.17%

Table 6: Hardness Testing

Sr.no	Formulation	Hardness (kg/cm2)
1.	F1 (-1, +1)	2.5
2.	F2 (+, +1)	1.8
3.	F3 (-1, -1)	1.3
4.	F4 (+1, -1)	3.9

Formulation F4 with code (+1, -1) shown hardness 3.9 (kg/cm2) which is more than other formulation hence, it is considered optimized formulation which will prevent the formulation from external damage

Ex-Vivo Studies

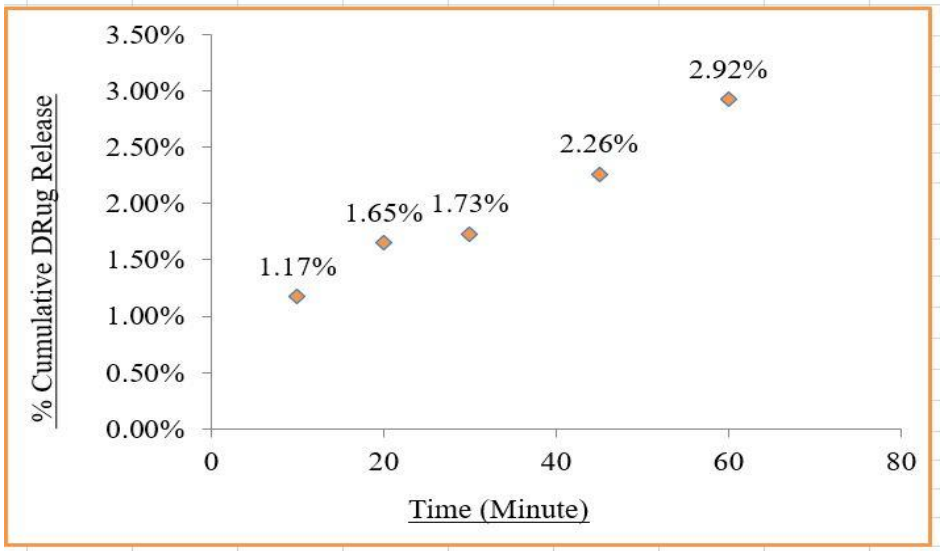
Figure 9. Franz Diffusion Cell

The above figure depicts the setup of Franz diffusion cell in which EX-Vivo buccal permeation study was performed.

The drug concentration calculated from the equation (1) given below,

Y =0.149X+0.016……..(1)

Figure10: Drug Concentration obtained from Ex-vivo Studies



The mean quantity of the drug, which is released from the optimized preparation after 10,20,30,45 and 60 minutes of munching[8], is taken from the receiver section and analyzed by the UV spectrophotometer. Percentage of drug release through the buccal mucosa at different time interval are shown in above graph. From the above graph the present release was found to be increasing with time indicating good permeation across the buccal membrane.

CONCLUSION

The layered chewing gum tablet of doxylamine succinate was successfully prepared by direct compression method. It is a cost-effective formulation and having a good patient compliance and bioavailability and It follow Zero Order Kinetics. According to the literature, it shows higher bioavailability than other routes of administration and having higher bioavailability than the other formulation. As a result, we formulate the medicated chewing gum because it has a quick onset of action and to lessen the effects of digestive problems. All the parameters found to be satisfactory; hence, the therapeutic dose of doxylamine succinate can be given in medicated chewing gum form with optimized formula, i.e., the code (+1, -1) from the factorial design. In order to mask the bitter taste and to increase the release of the drug from the formulation while chewing PVP and Eudragit polymer are incorporated in the formulation. Stability of Gum base are increased by the Layer Formulation around the Gum base. The study concluded that it is possible to Formulate Stable layered chewing gum of doxylamine succinate for prevention and treatment of nausea, vomiting related to pregnancy, allergy rhinitis and insomnia. We Compound the medicated Chewing gum without use of specialized instrument only by using conventional rotary punching machine which are easily available at laboratory scale.

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