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Research Article

Formulation Development and Evaluation of Amoxicillin Based Medicated Chewing Gum

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ABSTRACT

Introduction: Medicated Chewing Gum is considered as vehicle or drug delivery system to administer active principles that can improve health and nutrition. It is a novel drug delivery system containing masticatory gum base with pharmacologically active ingredient and intended to use for local treatment of mouth diseases or systemic absorption through oral mucosa. The buccal route of drug administration also has important advantage of direct access to the general circulation and overcomes the first pass hepatic metabolism. Methods and Materials: The aim of present study was to design and characterise Medicated Chewing Gum for the treatment of bacterial infection using Amoxicillin Trihydrate as model drug. The chewing gums were prepared using Health in Gum grade-01(HiG-01) as a directly compressible gum base developed by Cafosa (S.A.U.), Spain. The effect of concentration of (Base) Gum Base, (release modifier) Aerosil, and (antiadherant) talc was studied. Result and discussion: The dissolution study showed that optimum amount of Gum Base shows superior result. Amoxicillin Trihydrate is an antibacterial agent. After oral administration it is rapidly absorbed. Maximum peak plasma concentration is reached after approximately 1 hr this model drug is selected for the study in order to overcome the hepatic first-pass effect and there by possible reduction in the dose. The drug is tasteless so there was no issue with taste masking. Amoxicillin Trihydrate has higher oral bioavailability, less side effects and has short duration of action of about 1.02 hr; these factors make Amoxicillin Trihydrate is suitable candidate for formulation of medicated chewing gum used to treat bacterial infection.

INTRODUCTION

The dosage form or delivery system is critical to the success of a pharmaceutical product. Today chewing gum is gaining new consideration as drug delivery system it provides additional patient benefits and compliance, new competitive advantages from technological and marketing point of view. [1]

Inclusion of medicated chewing gum in the European Pharmacopoeia (under medicated chewing gum) in 1998 has further contributed to full acceptance. It takes time for a new drug delivery system to establish itself on the market and gain acceptance by both professionals and patients. Chewing gum is believed to manifest its position as a convenient and advantageous drug delivery system.

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Previously, chewing gum was mainly considered a confectionery product, however, fluoride chewing gum and especially nicotine chewing gum which was launched in the 1970s, paved the way for a more general acceptance of chewing gum as a drug delivery system. In addition to offering clinical benefits, chewing gum is attractive as it is a discrete and efficient drug delivery system as well as MCG provides patient a conventional mean of taking their medication. [2, 3]

Medicated chewing gums are defined by the European Pharmacopoeia and the guidelines for pharmaceutical dosage forms issued in 1991 by the Committee for Medicinal Products for Human Use (CPMP) as ''solid single dose preparations with a base consisting mainly of gum that are intended to be chewed but not swallowed, providing a slow steady release of the medicine contained''. According to European

pharmacopeia, 2002 medicated chewing gum is intended to be chewed for a certain period of time, required to deliver the dose, after which the remaining mass is discarded. During the chewing process, the drug contained in the gum product is released from the mass in to saliva and it could be absorbed through the oral mucosa or swallowed reaching the stomach for gastro-intestinal absorption, thus, two absorption pathways are possible to introduce the active ingredient, giving rise to a systemic effect. [4]

Empiric findings had shown that people chewing gum was better at keeping awake and alert, and that gum chewing eased tension. The acceptance of this somewhat anecdotally understood effect achieved a better scientific basis in the summer 2002 when L Wilkinson and co-workers published a study of 75 healthy volunteers who were led through a number of cognitive, recognition, and memory tests. The results provided the first evidence that the chewing of gum can improve episodic memory and working memory. [5]

The anecdotal effect of chewing gum on weight loss has also been studied recently. In December 1999, The New England Journal of Medicine revealed that while chewing gum, energy expenditure increases from 58 kcal per hour to 70 kcal per hour – an increase of 12%. The conclusion was that if a person chewed gum during walking hours, this alone would mean a yearly weight loss of more than 5 kg. Though there are many other interesting anecdotal effects that result from gum chewing, such as the easing of blocked ears. [6]

The advantages of utilizing a chewing gum drug delivery system are highlighted by T Imfeld in his 1999 review of gum chewing and oral health. There are two absorption pathways which are possible to introduce the active ingredient into the systemic circulation giving rise to a systemic effect. Drug absorbed directly via the buccal membrane avoids metabolism in the G.I tract & the first-pass effect of the liver; it might therefore be to administer a reduce dose in chewing gum compared to other oral delivery system. To obtain the optimal local effect to treat a health condition requires that the relevant active substance be available at a therapeutic level near or within the tissue being treated, regardless of the delivery system. For the treatment of oral cavity conditions, it is beneficial to achieve a therapeutic level of active substance in the saliva, and different formulations (e.g. oral gel, mouth rinse) have been created to meet this goal. Chewing gum is an ideal drug delivery system for this treatment area; the active substances are released as the gum is chewed, thus providing the potential for a high level of active substance to obtain local effect in the oral cavity. It is possible to design a chewing gum that releases active substances over a prolonged period. [7]

Systemic effects of active substances released from chewing gum can be achieved in two ways: in the "traditional" way, by swallowing the active substance, or buccally via absorption through the oral mucosa. The latter is of special interest. As buccal absorption avoids first-pass hepatic metabolism of the active substance, it could provide better bioavailability. Buccal absorption may also lead to fast onset of the active substance as the vascular supply of the buccal mucosa is rich and lead directly into the systemic circulation. Chewing gum promotes buccal absorption by releasing active substances at carefully controlled rates, thus allowing for extended exposure in the oral cavity. [8]

The objective of the present work is to formulate and develop medicated chewing gum delivery of Amoxicillin Trihydrate for bacterial infection. It is also planned to identify the important formulation parameters affecting the behaviour of medicated chewing gum. The buccal route of administration has the important advantage of direct access to systemic circulation. This advantage overcomes the first pass hepatic metabolism and local loss of the drug at sight. Amoxicillin Trihydrate is the suitable drug for local effect because it strongly binds to oral mucosa and secretes with saliva means continues local oral effect. This model drug is selected for study in order to reduce hepatic first pass metabolism and to improve systemic bioavailability and also possible reduction in dose.

MATERIALS AND METHODS

Materials Used in Formulation Development

Amoxicillin Trihydrate received as gift sample from Catchet Pharmaceuticals Pvt. Ltd. Bhiwadi, Rajasthan. Gum Base was received as a gift sample from Anshul Life Sciences, Mumbai (Cafosa gum, S.A.U., Spain), Aspartame received as gift sample from Alkem Pharmaceuticals, Mumbai. Talc, Aerosil® 200, Menthol, Titanium Dioxide, Microcrystalline cellulose were available at college and all the excipients were of analytical grade.

Experimental Methods

Formulation Development and Optimization

Table 1: Trial batches for selection and optimization of excipients

Ingredient (mg)	Batch Code			
	T1	T2	T3	T4
Amoxicillin Trihydrate	250	250	250	250
Health in Gum	620	660	700	760
Menthol	15	15	15	15
Sucrose	10	10	-	-
Aspartame	-	-	5	5
Aerosil	-	2	5	7
Talc	-	5	10	15
Titanium Dioxide	5	5	5	5
Avicel P-102	-	3	10	57
Total	900	950	1000	1100

Preparation of Medicated Chewing Gum

Procedure for Preparation of Medicated Chewing Gum of Amoxicillin Trihydrate by Using Direct Compression Method

Chewing gum Chewing gums were prepared by direct compression method. Amoxicillin Trihydrate, Health in Gum PWD-01, and menthol were mixed in porcelain mortar for sufficient period of time and passed through 100# sieve. This blend was mixed with colloidal silicon-dioxide, talc and Aspartame for 5 min and final blend was kept in freeze for 30 min. and processed for direct compression by using 12 mm round flat - faced punch of Single punch Chewing gum compression machine (Royal Artist). Compression force was kept constant for all formulations. Compositions of all batches are represented in Table 2 Pre-compression parameters of powder blend were performed [9-10].

EVALUATION

1. Identification and Characterization of drug [15]

a. UV spectrophotometer

To determine absorption maxima the UV spectrum of solution of Amoxicillin Trihydrate in phosphate buffer 6.8 was scanned at 400 nm to 200 nm.

b. FTIR Spectroscopy

The drug was subjected to FTIR studies for the purpose of characterization. Drug was mixed with potassium bromide in 1:100 proportions and spectrum was r ecorded in range of 400-4000cm^{-1}. Potassium bromide was used as a blank while running spectrum.

2. Compatibility Studies

Excipients were mixed with the drug in 1:1 ratio. These samples were then subjected to IR and DSC analysis as a part of compatibility studies.

a. FTIR Spectrum

The physical mixture of final formulation was subjected to FTIR studies for the purpose of compatibility. Mixture was mixed with potassium bromide in 1:100 proportions and spectrum was recorded in range of 400- 4000cm^{-1}. Potassium bromide was used as a blank while running spectrum.

b. Differential Scanning Calorimetry

The DSC thermogram of the pure drug was recorded using Mettler TIodo by Zurich, Switzerland differential scanning calorimeter with liquid nitrogen cooling accessory. 10 mg of sample and alumina was heated in a closed pierced aluminium pan from 0ºC to 400 ºC at a heating rate of 10 ºC /min under a stream of nitrogen at a flow rate of 100 mL / min.

2. Granule properties

The powder blends of all the six formulations were studied for their granule properties such as Angle of Repose, Bulk Density, Tapped Density, Compressibility Index, Hausner's Ratio.

3. In-process Parameters [13, 14]

a. Thickness

Ten chewing gums of each batch were picked randomly and its thickness was measured individually using Digimatic calliper. The values of thickness were used to adjust the initial stages of compression.

b. Weight Variation

The weight variation test of the batches was done as per the guidelines of IP. Twenty Chewing gums were randomly selected, weighed and the mean weight was calculated. Percentage deviation of each chewing gum from the mean was calculated.

c. Hardness

The hardness of the chewing gum was measured by Monsanto Hardness Tester in kg/cm2. Ten chewing gums were randomly picked from each formulation and mean and the standard deviation values were calculated for each batch.

d. Friability

Roche friabilator was used for testing the friability using the following procedure. Six chewing gums were weighed accurately and placed in the tumbling apparatus that revolves at

Table 2: Formulation of Amoxicillin Trihydrate chewing gum Chewing gum

Ingredient (mg)	Batch Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Amoxicillin Trihydrate	250	250	250	250	250	250	250	250	250
Health in Gum	800	760	780	760	760	780	800	780	800
Menthol	10	10	10	10	10	10	10	10	10
Aspartame	5	5	5	5	5	5	5	5	5
Aerosil	7	7	7	7	7	7	7	7	7
Talc	20	15	15	20	10	20	15	10	10
Titanium Dioxide	5	5	5	5	5	5	5	5	5
Avicel P-102	3	48	28	43	53	23	8	33	13
Total	1100	1100	1100	1100	1100	1100	1100	1100	1100

25 rpm dropping the chewing gums through a distance of six inches with each revolution. After 4 minutes, the chewing gums were weighed and the percentage loss in the weight was determined. The value was expressed as a percentage.

4. Finished Product Parameters

a. Content Uniformity Test

Ten chewing gums were selected randomly. Each chewing gum was soaked into a 50 mL volumetric flask containing phosphate buffer pH 6.8 and heated for 30 minutes to soften the gum. The soft mass was then crushed and the solution was sonicated for 30 minutes with the heater on. The solution was then cooled and centrifuged for 30 minutes for complete extraction of the drug from the soft mass of the gum. The supernatant solution was then filtered and analyzed for the content of Amoxicillin Trihydrate using UV spectrophotometer (Jasco- V630, Japan). The absorbance was measured by double beam UV-Visible spectrophotometer at λmax of 272 nm.

b. In vitro Dissolution Study [11, 12]

R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Dhule, have specially developed chewing gum dissolution test apparatus (which is under patent) for *in vitro* release testing of medicated chewing gums. Dissolution test of Chewing gums were performed using Phosphate buffer 6.8 as dissolution medium. Test sample (2 ml) was withdrawn at particular time interval (2, 4, 6, 10, 12 min) and replaced with fresh dissolution medium maintained at 37 ± 1 ^{0}C. The samples were filtered (membrane filter, 0.45µm) and analyzed using a UV spectrophotometer at λ_{max} 272nm.

Table 2a: Details of Test

Dissolution test apparatus	Medicated Chewing Gum Dissolution apparatus
Speed	56 strokes per min
Volume of medium	40 ml
Sample withdrawal at each time interval	2 ml
Medium used	Phosphate Buffer (pH6.8)
Temperature	37±0.5ºC

c. Stability Studies

Stability of a drug has been defined as the ability of a particular formulation, in a specific container to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of various environmental factors such as temperature, humidity and light. It also suggests storage conditions, retest period and shelf life. Stability studies were carried out at 40 ± 2 ^{0} C and 75 % Relative humidity (RH) for a specific time period up to 30 days using environmental test chamber (Remi)for optimized formulation. Samples were evaluated for drug content, weight variation, hardness, thickness friability, and *in-vitro* drug release.

RESULTS AND DISCUSSION

Standard Calibration Curve of Amoxicillin Trihydrate in Phosphate Buffer pH 6.8

Major functional groups present in Amoxicillin Trihydrate showed characteristic peaks in the FTIR spectrum. The major peaks are identical to the functional group of Amoxicillin Trihydrate,

Hence the sample was confirmed as Amoxicillin Trihydrate.

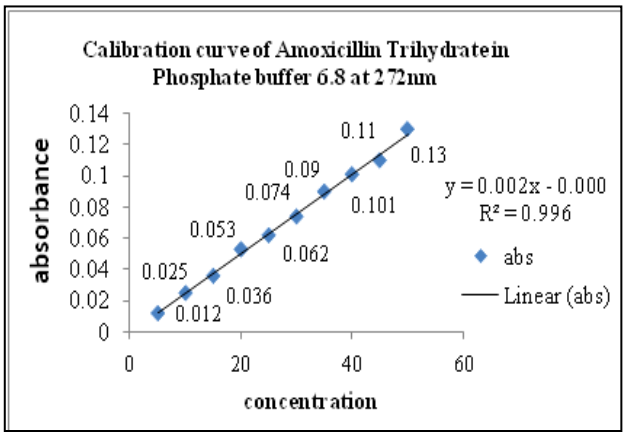

Figure 1: Calibration curve of Amoxicillin Trihydrate in phosphate buffer (pH 6.8)

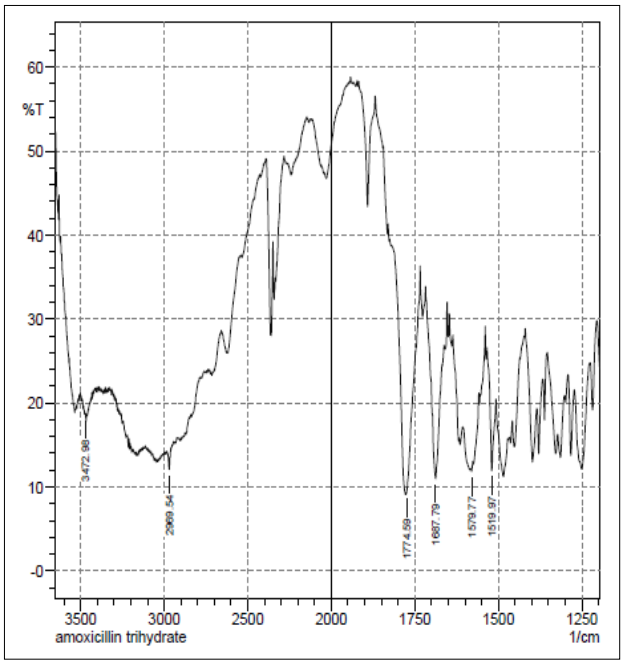

Figure 2: FTIR spectrum of Amoxicillin Trihydrate

The results revealed no significant change in peak pattern in the IR spectra of pure drug and combination of drug with excipient, indicating no interaction between pure drug and excipients. The overlapped FTIR spectra of drug and physical mixture of formulation is shown in Fig. 3.

Evaluation Parameters of Trial Batches

The trial batches were prepared as shown in the Table 1 the excipients were optimized by an individual problem to solution approach. The results obtained are shown in the following tables. From those results the suitable levels of the formulation excipients were selected.

Table 2b: Functional groups observed in Amoxicillin Trihydrate

Sr. No.	Functional Group	Standard Ranges (cm^{-1})	Observed Ranges (cm^{-1})
1	O-H (Stretching)	3550-3400	3472
2	NH_3^+	3200-2500	2909
3	β-lactum C=O(Stretching)	1776	1774
4	Amide C=O(Stretching)	1688	1687
5	COO^- Asymmetric Stretching	1582	1579
6	Aromatic ring	1519	1519

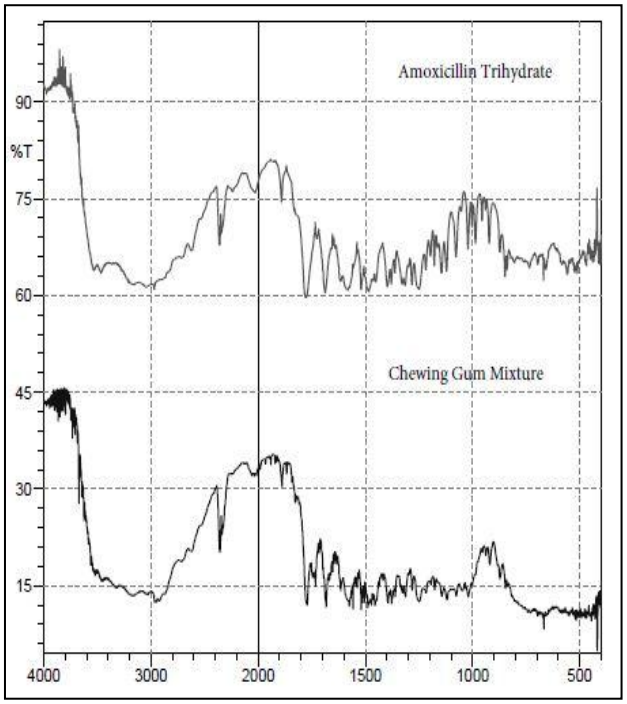

Figure 3: FTIR spectra of Amoxicillin Trihydrate and Chewing Gum Mixture overlapped.

Tablet 2c: Evaluation of Trial Batches

Sr. No.	Batch code	Problems observed	Solution
1	T1	Sticking to the die and Picking by punches	Addition of flow promoter and lubricant
2	T2	Sticky powder blend due to moisture absorption by sucrose	Change the sweetener
3	T3	Poor flow properties	Increase the concentration of glidant
4	T4	Hard to the eject compressed dosage form	Increase the concentration of Gum base

Table 3: Pre-compressional Properties of Powdered Blend

Batch code	Bulk density* (g/mL)	Tapped density* (g/mL)	Angle of repose*(ɵ)	Carr's Index* (%)	Hausner's ratio*
F1	0.69±0.01	0.81±0.01	26.39±0.03	14.81±0.02	1.17±0.01
F2	0.71±0.03	0.83±0.03	25.11±0.01	14.45±0.07	1.16±0.03
F3	0.63±0.01	0.86±0.02	27.36±0.07	26.74±0.05	1.36±0.01
F4	0.71±0.04	0.85±0.04	28.10±0.05	16.47±0.1	1.19±0.06
F5	0.77±0.09	0.87±0.01	27.11±0.04	11.49±0.02	1.12±0.05
F6	0.76±0.02	0.86±0.01	29.50±0.01	11.62±0.01	1.13±0.04
F7	0.69±0.01	0.85±0.02	26.16±0.02	18.82±0.04	1.23±0.05
F8	0.70±0.03	0.83±0.05	28.25±0.05	15.66±0.05	1.18±0.06
F9	0.71±0.03	0.87±0.04	25.32±0.06	18.39±0.05	1.22±0.03

All values are expressed as mean± SD; *=3,

Table 4: In-Process Parameters of Amoxicillin Trihydrate Chewing Gum

Batch code	Hardness* (kg/cm^2)	Friability** (%)	Weight variation. ***(mg)	Thickness* (mm)	Drug content# (%)
F1	3.46± 0.05	0.41±0.01	1092.8±0.88	6.36±0.01	97.45±0.08
F2	3.73 ± 0.15	0.31±0.01	1096.3±0.94	6.31±0.01	96.59±0.05
F3	3.83 ± 0.11	0.42±0.01	1098.5±0.97	6.42±0.01	99.11±0.02
F4	3.70 ± 0.10	0.23±0.01	1094.5±0.97	6.54±0.02	96.09±0.02
F5	3.66 ± 0.05	0.44±0.01	1089.1±0.97	6.52±0.02	97.08±0.04
F6	3.83 ± 0.05	0.32±0.01	1097.5±0.85	6.51±0.01	99.02±0.09
F7	3.76 ± 0.06	0.36±0.01	1089.3±0.93	6.54±0.01	99.64±0.02
F8	3.73±0.12	0.44±0.01	1097.5±0.93	6.52±0.02	98.04±0.08
F9	3.25±0.15	0.24±0.01	1099.8±0.92	6.45±0.02	101.57±0.02

All values are expressed as mean ±SD; *n=10, **n=6, ***n=20, #n= each value represents as singly. Where n = no of tablets

Table 5: *In Vitro* Drug Release

Batch code	Percent drug release with ±S.D.						
	Time (in minutes)						
	0	**2**	**4**	**6**	**8**	**10**	**12**
F1	0	13.52±0.04	23.46±0.09	38.72±0.06	47.92±0.04	67.8±0.11	88.74±0.06
F2	0	12.64±0.06	23.64±0.08	37.8±0.12	46.72±0.11	64.22±0.09	82.98±0.06
F3	0	13.44±0.07	25.84±0.06	38.5±0.11	46.64±0.13	66.92±0.09	85.48±0.04
F4	0	9.76±0.11	22.6±0.03	36.52±0.04	47.76±0.02	61.12±0.02	80.32±0.06
F5	0	14±0.09	25.42±0.07	34.66±0.09	46.64±0.06	64.76±0.13	84.54±0.12
F6	0	14.16±0.01	26.26±0.03	39.46±0.08	48.16±0.09	67.06±0.02	86.68±0.03
F7	0	15.36±0.05	34.4±0.04	49.88±0.08	65.2±0.11	82.14±0.12	90.24±0.09
F8	0	11.68±0.09	26.44±0.04	42.6±0.08	55.9±0.07	71.52±0.15	87.04±0.12
F9	0	15.68±0.07	34.88±0.16	50.62±0.07	66.24±0.05	83.32±0.09	**92.56±0.13**

As seen in Table 3, low Hausner's Ratio (>1.1), Compressibility Index (>13) and Angle of Repose (>37) values indicated good flow property. The values for all batches were found to be within the permissible limits as mentioned in USP and IP.

As seen in Table 4, the hardness for all the formulations was maintained between 3-4 kg/cm^2 which was considered to be minimum for compressed chewing gums. The % friability for all the formulations was found to be less than 1% indicating that the friability for the chewing gums was within the prescribed limits. From the results mentioned in Table 5, it was seen that F9 showed highest drug release of 92.56% at the end of 12 minutes.

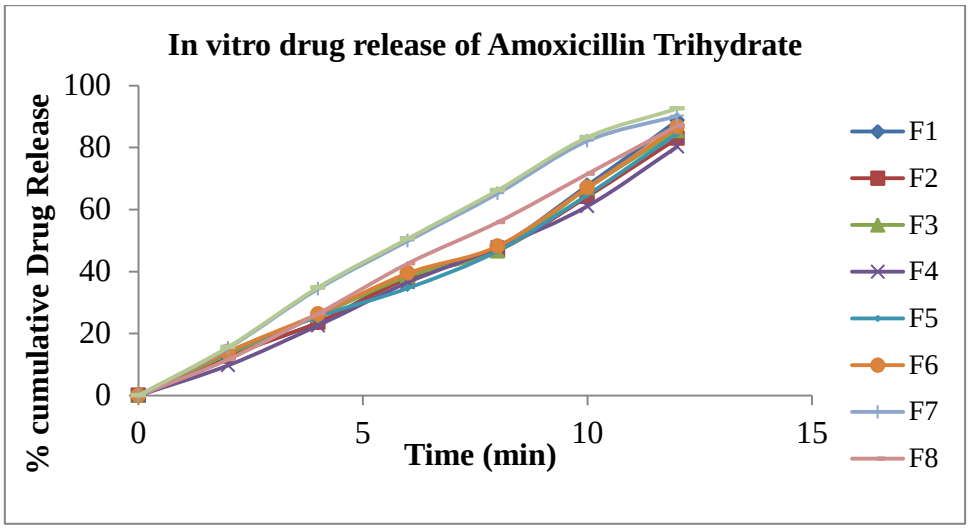

Figure 4: Graphical Representations of *In- Vitro* Dissolution Study of All Batches

The results of the stability studies for optimized batch are mentioned in the Table 6. There was no variation seen in the physical appearance of the optimized batch medicated chewing gums when they were stored for a period of 30 days under the accelerated conditions of 40 ºC ± 2ºC temperature and 75% ± 5%RH humidity. The tabulated stability data revealed that there was no significant change observed in the parameters studied; indicating that the optimized batch was stable at the experimented conditions.

Table 6: Effect of Temperature and Humidity on Optimized Batch after Stability

Parameters	Results obtained at 0 days	Results obtained after 30 days
Appearance	Smooth	Smooth
Hardness (kg/cm^2)	3.25 ± 0.28	3.87±0.08
Friability (%)	0.686 ± 0.05	0.668±0.01
Weight variation (mg)	1092.05 ± 0.74	1092.05±0.71
Drug content (%)± SD	101.04 ± 0.82	99.96±0.76
In-vitro drug release± SD	92.56±0.13	92.34±0.21

CONCLUSION

Thus, it was concluded that it was possible to formulate medicated chewing gums of antibacterial drugs such as Amoxicilin Trihydrate. Bioavailability studies can also be conducted to check the *in-vivo* performance of the medicated chewing gums. The new products can be developed using this drug delivery system which will offer differentiation in the market place and will offer advantages like patient compliance, low costs and most importantly flexibility to the formulator due to simple product mix without compromising on safety and efficacy.

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