Research Article

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International Journal of Drug Development and Research

2021
Vol.13 No.3:6085

Formulation Developement & Evaluation of Atenolol Based Medicated Chewing Gum

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Received date: September 09, 2020; **Accepted date:** August 13, 2021**; Published date:** August 24, 2021

Citation: Bagdane A (2021) Formulation Developement & Evaluation of Atenolol Based Medicated Chewing Gum. Int J Drug Dev & Res Vol.12 No.3.

ABSTRACT

Aim

Formulation development & Evaluation of Atenolol based Medicated Chewing gum.

Context

The medicated chewing gum formulations are helpful for fast onset of action.drug relase due to mastication process.direct access to the general circulation and overcomes the first pass hepatic metabolism.

Objective

The objective to develop the formulation & evaluate medicated chewing gum as specialised drug delivery system.improved bioavaibility & patient compliance. Methods & Materials

Medicated chewing gum were prepared by Direct compression method 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 ,(released modifier) Aerosil, and (antiaderant) talc was studied with the study of potential factors affecting drug release by 32 full factorial experimental design.

Results and Discussion

The dissolution study showed that optimum amount of gum base shows superior result.Atenolol is an antihypertensive agent.After oral administration it is rapidly absorbed. Developed medicated chewing gum Evaluated for the charecterstics like FTIR,DSC & the evalution of tablets i.e. diameter, thickness, friability, hardness, average weight, content uniformity,stickiness and dissolution study were performed. A 32 full factorial design was selected and the 2 factors were evaluated at 3 levels. The concentration of Polymer(X1) and concentration of Talc (X2) were selected as independent variables and the dependent variables were Hardness & percent drug release at 12 min .F4 batch are optimised having percent drug release 92%.optimised batch for 1 month accelerated stability studies was performed. Stat-Ease Design Expert 11.0.Conclusion: The developed formulation of medicated chewing gum can be a better alternative to mouth dissolving and conventional tablet formulation. It may be proved as a promising approach to improve the bioavailability as well as to improve patient compliance.

Keywords: Atenolol, Health in gum base, Talc, Direct compression method

INTRODUCTION

Medicated chewing gum is solid, single-dose preparation that is intended to be chewed for a certain period of time,deliver the drug and which may contain one or more than one active pharmaceutical ingredient .The drug product is intended to be chewed in the oral cavity for a specific period of time,after which the insoluble gum base is discarded.Many therapeutic agents are absorbed in the oral cavity. Medicated chewing gums are defined by the European Pharmacopoeia and guidelines for pharmaceutical dosage forms issued in 1991 by the committee for medicinal products for Human use(CPMP) as solid single dose preperations with a base consisting mainly of gum that are intended to be chewed but not to be swallowed,providing a slow steady release of the medicine contained.The drug product is intended to be chewed in the oral cavity for a specific period of time after which the insoluble gum base is discarded Atenolol is one of the most widely used β-blockers in the United Kingdom and was once the first-line treatment for hypertension. Atenolol is effective at reducing blood pressure, but recent studies indicate that it does not reduce the morbidity or mortality caused by hypertension, and may even increase mortality in some subgroups. Atenolol is a so-called beta1-selective (or 'cardioselective') drug. That means that it exerts greater blocking activity on myocardial beta1-receptors than on beta2 ones in the lung. The beta2 receptors are responsible to keep the bronchial system open. If these receptors are blocked, bronchospasm with serious lack of oxygen in the body can result. However, due to its cardioselective properties, the risk of bronchospastic reactions. [1]

This drug delivery system provides additional patient benefits and compliance, offering several advantages over tablets or liquid formulations in that, the therapeutic system is not be swallowed and this increases patient compliance, especially for geriatrics and paediatrics with swallowing disorders; moreover, the product can be taken anywhere and at any time as it does not require liquids to aid swallowing. Most of the drug released from the gum through mastication is rapidly absorbed via the buccal cavity due to large vascularisation; therefore, a faster absorption results in a shorter duration of action. Alternatively, drug released from medicated chewing gum which is not absorbed through the oral cavity membranes will be swallowed and reach the stomach in a very fine dispersed form, thus being easily available for gastro-intestinal absorption with a consequent fast onset of action. The oral mucosa is highly perfused with blood vessels having a blood flow of 20-30 ml/min for each 100g of tissue. Drugs absorbed via the buccal cavity have direct access to the systemic circulation which bypasses intestinal and hepatic first-pass metabolism, thus potentially increasing their extent of absorption. Therefore it might be possible to administer a reduced dose in chewing gum in contrast to other oral drug delivery systems. [2]

EXPERIMENTAL

Materials

Atenolol (drug) obtained from Ipca pharmaceutical Ltd. Mumbai, Health in Gum Base obtained from Ansul Life Sciences,Mumbai and talc, Aspartame,Avicel PH-102,Aerosil from MET BKC,Nashik.

Methods

Direct Compression Method

Chewing gum Chewing gums were prepared by direct compression method. Atenolol(Drug), Health in Gum PWD-01(Polymer), and menthol(Cooling Agent) were mixed in porcelain mortar for sufficient period of time and passed through 22# sieve. This blend was mixed with Titanium dioxide(oficifier),Talc(Antiadherant), Aerosil(Glident), Avicel PH-102(Diluent) and Aspartame(Sweetner) for 5 min and final blend was processed for direct compression by using 10×12 mm round Oval shaped punch of Single punch Chewing gum compression machine. Compression force was kept constant for all formulations. Composition of all batches are represented in Table 6 Precompression parameters of powder blend were performed. [3]

Factorial Design Experiment

A 32 full factorial design was employed to evaluate the effect of each of the selected variables and their interactions on the response. The amount of Polymer (Gum base) (X1) and Talc (X2) were selected as the independent variables i.e. factors. The levels of these factors were selected on the basis of initial studies and observations. All the other formulation aspects of processing variables were kept invariant throughout the study period. The data were analyzed by using Design Expert Software 11.0.0. Table 1 summarizes the experiment runs and their factor combinations used. In this study factorial design based on the response surface method was adopted to optimize effective factors for the release of the drug from the Medicated chewing gum.

Independent Variables: X1 Polymer (Gum Base), X2 Talc Dependent Variable:Y1 Hardness, Y2 = Release after 12 min. The matrix of the design including investigated responses ,i.e.% drug release, Hardness are shown in Table1. The results obtained were analyzed by Design Expert Software 11.0.0. The results for data optimization of experimental matrix are shown in result and discussion. All the formulations were prepared as per the procedure used for the preliminary formulations and evaluated for various parameters.[4]

Std	Run	Block	Factor 1 Conc. Of Gum base mg	Factor 2 Conc. Of Talc Mg	Response 1 Hardness(kg/Cm2)	Response 2 Drug Release(%)
9	1	Block 1	800.00	30	3.12±0.05	89.02±0.06
3	2	Block 1	800.00	25	3.32±0.15	79.06±0.06
7	3	Block 1	800.00	20	3.77±0.11	81.18±.0.04
2	4	Block 1	780.00	30	3.36±0.10	92.12±.0.06
8	5	Block 1	780.00	25	3.15±0.05	84.42±.012
1	6	Block 1	780.00	20	3.68±0.05	89.63±.003
5	7	Block 1	760.00	30	3.23±0.06	93.16±0.09
6	8	Block 1	760.00	25	3.23±0.12	87.02±0.12
4	9	Block 1	760.00	20	3.65±0.15	87.89±0.13

Table 1: Experimental Design of the Optimization step for Formulations.

Represents mean ± S.D. (n = 3)

Trail Batch	T1	T2	T3	T4	T5	T6
Atenolol	25	25	25	25	25	25
Polymer (Health in Gum-01)	630	650	700	730	760	800
Menthol	15	15	15	15	15	15
Sucrose	10	-	-	-	-	-

Aspartame	-	10	10	10	10	10
Aerosil	-	10	10	10	10	10
Talc	-	15	20	25	25	25
Titanium Dioxide	5	10	10	10	10	10
Avicel P-102	15	30	50	25	50	10
Total	700	800	840	850	900	900

Table 2: Formulation Development of trial batches for selection & optimization of excipients.

Sr. No.	Batch Code	Observation	Solution
1	T1	Stuck to the die and Picked up by punches	Addition of flow promoter and lubricant
2	T2	Sticky powder blend due to moisture absorption by sucrose	Sweetener was changed
3	T3	Poor flow properties	Increased the concentration of glidant
4	T4	Poor flow properties	Increased the concentration of glidant
5	T5	Hard to the eject compressed dosage form	Increase the concentration of Gum base.
6	T6	Hardness of chewing gum more.reduced the hardness of tablet.	Increase the concentration of Gum base.

Table 3: Observation by trail batches.

Trail batches are finally concluded by next optimization T5,T6 Batch are selected.

Batch Code Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Atenolol	25	25	25	25	25	25	25	25	25
Health in Gum	800	800	800	780	780	780	760	760	760
Menthol	5	5	5	5	5	5	5	5	5
Aspartame	10	10	10	10	10	10	10	10	10
Aerosil	10	10	10	10	10	10	10	10	10
Talc	30	25	20	30	25	20	30	25	20
Titanium Dioxide	10	10	10	10	10	10	10	10	10
Avicel P-102	10	15	20	30	35	40	50	55	60
Total	900	900	900	900	900	900	900	900	900

Table 4: Formulation of Atenolol chewing gum Chewing gum.

Identification and Characterization of Drug[5]

UV Spectrophotometer

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

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR study of Atenolol was carried out to identify the functional group present in material. For FTIR spectroscopy, samples were dried and sample and KBr were mixed ratio 1:100. The method used was Diffused Reflectance Spectroscopy (DRS). Then the IR spectrum was taken by FTIR spectrophotometer (IR Affinity 1, Shimadzu, Japan).

Differential Scanning Calorimetry (DSC) Analysis

Thermogram of Atenolol was obtained using Mettler TIodo by Zurich, Switzerland Differential Scanning Calorimeter using aluminum pans. Nitrogen was purged through cooling unit. Indium standard was used to calibrate the DSC temperature. The samples were hermetically sealed in aluminum pans and heated at a constant rate of 10oC/min, over a temperature range of 0 to 400oC. Inert atmosphere was maintained by purging nitrogen at the flow rate of 100 mL/min.

Evaluation of Precompression parameters of powdered Blend [6]

Angle of Repose

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose was determined by the funnel method. A glass funnel was secured with its tip at a given height (H) above a piece of graph paper placed on a horizontal surface. Powder was poured through the funnel until the apex of the conical pile touched the tip of the funnel. .

Bulk Density

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape and the tendency of the particles to adhere to one another. The sample equivalent to 10 g was accurately weighed and filled in a 50 ml graduated cylinder and the powder was levelled and the unsettled volume, (V0) was noted.

Tap Density

The tapped density was determined by mechanically tapping the measuring cylinder or by using the digital bulk density tester and the tapped volume was noted. .

Hausner's Ratio

Lower Hausner's ratio = better flowability.

Higher Hausner's ratio = poor flowability.

Evaluation of Post Compression Parameters of Medicated Chewing Gum [6]

Thickness

Thickness and diameter test permit accurate measurement and provides information on the variation between Chewing gums. Three Chewing gums were taken and the thickness and diameter was measured using a digital Vernier Caliper (Make/ Model-Dial Calliper/Advance) The Chewing gum thickness and diameter was controlled within a 5% variation of a standard value.

Hardness

Hardness indicates the ability of a Chewing gum to with stand mechanical shocks of handling in manufacturing, packaging and shipping. The hardness of the Chewing gums was determined using Monsanto Hardness Tester (Make/Model-Dolphin,Country-India) The force needed to disrupt them by crushing in kg/cm2. Chewing gums were randomly picked from each formulation batch and the mean and standard deviation values were calculated.

Friability

Friability is the measure of Chewing gum strength. Roche Friabilator as used for testing the friability using the following procedure. This test subjects a number of Chewing gums to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the Chewing gums to a distance of 6 inches in each revolution. A sample of pre-weighed 6 Chewing gums was placed in Roche friabilator (Make/Model-Meta Lab,Country-Ahmedabad (india) which was then operated for 100 revolutions i.e. 4 minutes. The Chewing gums were then dusted and reweighed. A loss of less than 1 % in weight in generally considered.

Weight Variation Test

To find out weight variation, 10 Chewing gums of each type of formulation were weighed individually using an electronic balance, average weight was calculated and individual Chewing gum weight was then compared with average value to find the deviation in weight. [7]

Chemical Parameters

Drug content Uniformity Test

Atenolol chewing gum from each batch was tested for their drug content. Place one MCG in required XmL of solvent or mixture of solvent (as per complete solubility of drug substance), crush the MCG with a glass rod or spatula after approximately 30 minutes of soaking with heating when it is sufficiently soft. Afterwards continue vigorous stirring with the aid of ultrasound minimum for 60 minutes for complete extraction. Filter through a 0.45-µm membrane filter and analyzed for the content of Atenolol using UV spectrophotometer (Shimdzu). The absorbance was measured at wavelength 225nm using double beam UV-Visible spectrophotometer. [8]

In Vitro Dissolution Study

R.C. Patel Institute of Pharmaceutical Education and Research have specially developed chewing gum dissolution test apparatus (which is under patent) at 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 ± 0.5 0C. The samples were filtered (membrane filter, 0.45µm) and analyzed using a UV spectrophotometer at λmax 225nm.[8]

Stability Studies: (ICH Guideline)

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 for optimized formulation. Samples were evaluated for drug content, weight variation, hardness, thickness and friability.

Results and Discussion

Statistical Analysis

The aim of present work was to achieve optimized formulations determining the effects of some important factors during the process preparation on Medicated Chewing Gum physiochemical properties. Mean while the Medicated Chewing Gums were being processed; the impact of different factors had been evaluated by making changes in their quantity. Finally, two of the most significant factors had been chosen as the independent variables. In the next step, for determining the low and high levels of each factor, the formulations were made, and the results. According to design-Expert and considering these two variables, an experimental matrix was performed in which 9 experiments were performed These models were evaluated statistically by applying one-way ANOVA ($p<0.05$). All the responses studied were largely affected by the variables chosen as reflected from the results of regression analysis and ANOVA.

The Model F-value of 334.61 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise.
Values of "Prob > F" less than 0.0500 indicate model terms are significant.

The final models in terms of coded and actual factors are,

Hardness (coded factors) = +3.27+0.0167 *A-0.1158 *B - - - - - - - - (1)

Hardness (actual factors) = +3.89+00083 *Polymer -0.0463 *Talc- - - - (2)

From equation (1), it was concluded that Polymer (factor A) and Talc (factor B) had individual effect on drug release.

According to the obtained results, the developed models are statistically accurate and can be used for further analysis

The Model F-value of 9.94 implies the model is significant. There is only a 4.38% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case B2 is a significant model terms.Value is greater than 0.1000 indicatethe model terms are not significant.

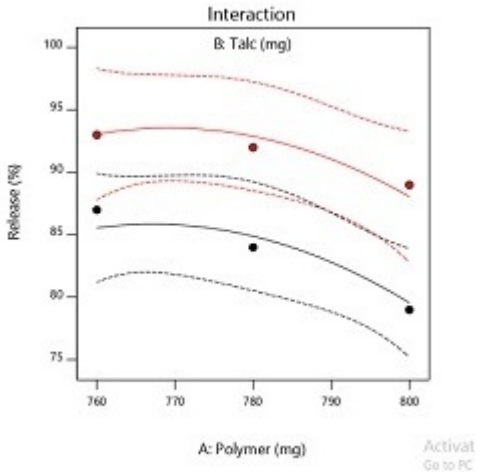

Figure 1: Interaction plot for Hardness.

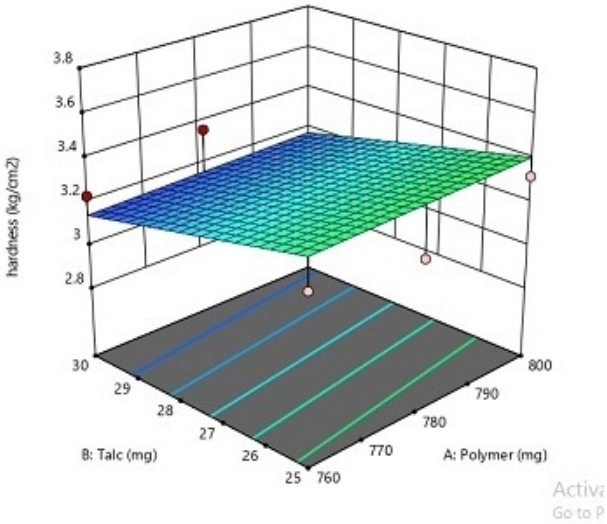

Figure 2: Three Dimensional View of Hardness.

Use a 3D surface plot to see how a response variable relates to two predictor variables. A 3D surface plot is a three-dimensional graph that is useful for investigating desirable response values and operating conditions. The 3D surface consist the variations in the concentration ranges for Gum Base (Polymer) and Talc for their best fitted model for optimized formulations. The 3D surface shows that as the concentration of Gum Base and Talc increases the Hardness of formulation also increases.

The predicted R2 of 0.3533 is is not close the Adjusted R2 of 0.8481; i.e. the difference is less than 0.2. Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 9.006 indicates an adequate signal. This model can be used to navigate the design space.

The final models in terms of coded and actual factors are,

Drug release (coded factors) RE = +87.60-2.75 *A+4.00 *B +0.25*AB-2.33 *A^2+1.29*B - - - - - - - (3)

Drug release (actual factors) RE = -3134.61+8.825*Polymer-13.66*Talc +0.005*Polymer*Talc-0.0058 Polymer² +0.2066*Talc² - - (4)

From equation (3), it was concluded that Polymer (factor A) and Talc (factor B) had individual effect on drug release.

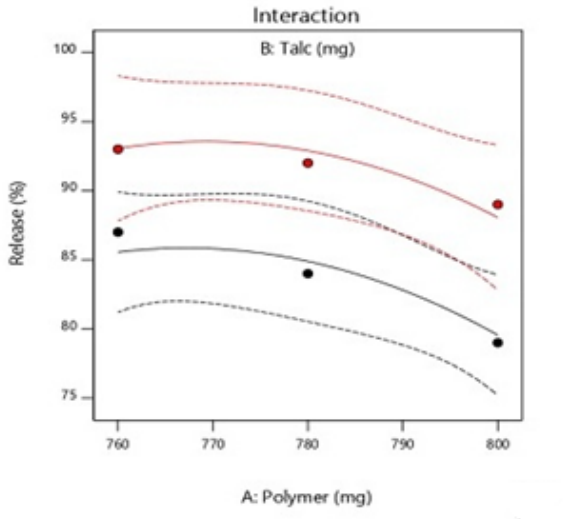

Figure 3: Interaction plot for Drug Release.

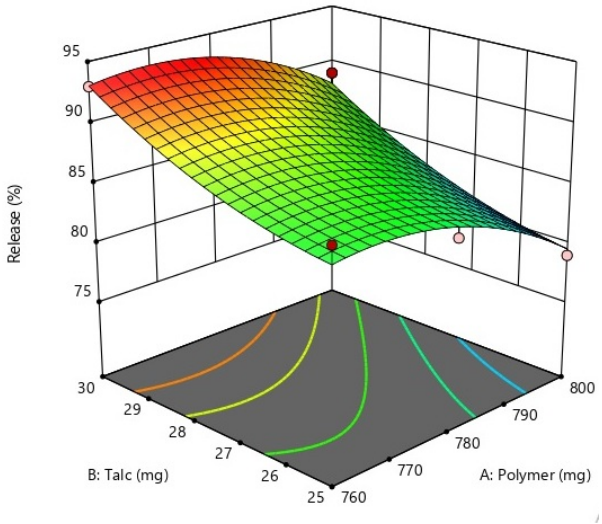

Figure 4: Three dimensional plot for Drug Release.

3D surface plot to see how a response variable relates to two predictor variables. A 3D surface plot is a three-dimensional graph that is useful for investigating desirable response values and operating conditions. The 3D surface consist the variations in the concentration ranges for Gum base (Polymer) and Talc for their best fitted model for optimized formulations. The concentration of Gum Base (Polymer) and Talc was at low level and at the drug release was less. At medium range concentration of Gum Base (Polymer) and Talc the drug release was more as compare to low concentration level and high concentration level.

Fourier Transform Infrared Spectroscopy (FTIR)

Drug,polymer,&Physical mixture of final formulation interactions were studied by FT-IR spectroscopy. Infrared spectrum of pure drug, polymer & Physical mixture of final formulation were obtained with the help of potassium bromide to monitor structural changes of Chewing gum Formulation.

The results revealed no significant change in peak pattern in the IR spectra of pure drug,Polymer and combination of drug with excipients.indicating no ineraction between pure drug,polymer,and excients.The overlapped FTIR spectra of drug,Polymer and physical mixture of formulation is shown in Fig.5.

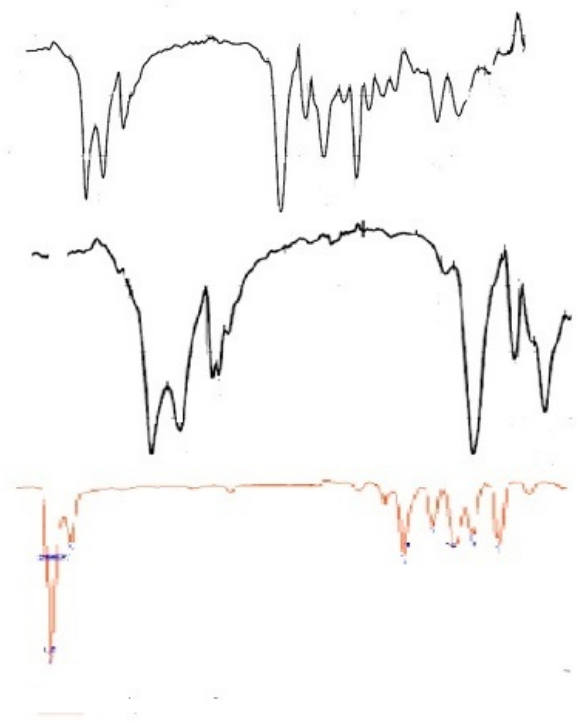

Figure 5: FTIR Spectra of Atenolol, Polymer, & Physical Mixture of final formulation.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimeter was performed using aluminium pans. Nitrogen was purged through cooling unit. The samples were hermetically sealed in aluminium pans and heated at a constant rate of 10oC/min, over a temperature range of 0 to 400oC. Inert atmosphere was maintained by purging nitrogen at the flow rate of 100 mL/min.

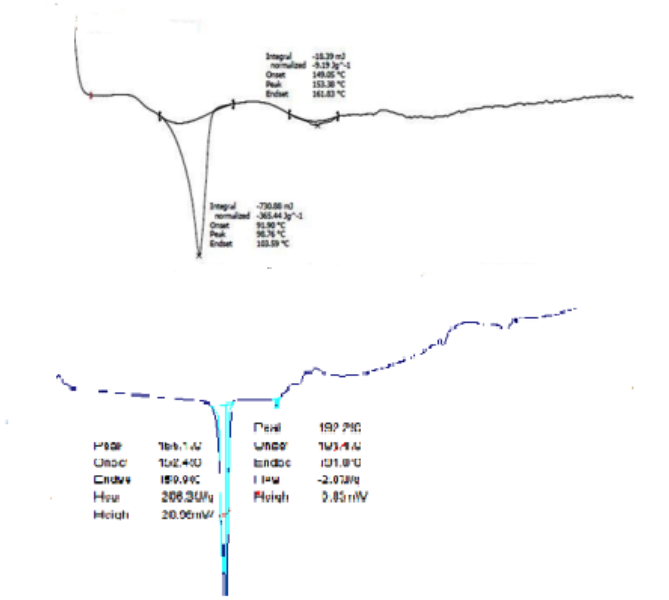

Figure 6: DSC Spectra of Atenolol and Formulation overlapped.

The melting of Drug peak is been shifted towards 156oC. There is exothermic peak at 98.76 oC indicate appearance in case of gum base due to it polymeric amorphous state. Thus it was proved that there were no major difference in Thermograms, hence the excipients were compatible with the drug chosen and so could be safely used to formulate medicated chewing gum. Thus indicate a drug & physical mixture does not form a complex but acts as physical mixture.

Pre (Before) compression parameters of powdered Chewing gum blend mixture

Batch Code	Bulk density* (g/mL)	Tapped density* (g/mL)	Angle of repose*(e)	Carr's Index* (%)	Hausner's ratio*
F1	0.76±0.02	0.86±0.01	29.50±0.01	11.62±0.01	1.13±0.04
F2	0.69±0.01	0.85±0.02	29.24±0.02	23.18±0.04	1.23±0.05
F3	0.70±0.03	0.83±0.05	28.36±0.05	15.66±0.05	1.18±0.06
F4	0.71±0.04	0.85±0.04	28.36±0.05	16.47±0.1	1.19±0.06
F5	0.71±0.03	0.87±0.04	27.47±0.06	18.39±0.05	1.22±0.03
F6	0.69±0.01	0.81±0.01	27.02±0.03	14.81±0.02	1.17±0.01
F7	0.71±0.03	0.83±0.03	28.31±0.01	14.45±0.07	1.16±0.03
F8	0.63±0.01	0.86±0.02	29.24±0.07	26.74±0.05	1.36±0.01
F9	0.77±0.09	0.87±0.01	27.11±0.04	11.49±0.02	1.12±0.05

Table 5

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

Post(After) compression Parameters Atenolol chewing Gum

Batch code	Hardness* (kg/cm2)	Friability** (%)	Weight variation. ***(mg)	Thickness* (mm)	Drug content# (%)
F1	3.12± 0.05	0.41±0.01	899±0.88	6.36±0.01	96±0.02
F2	3.32 ± 0.15	0.31±0.01	900±0.94	6.31±0.01	97.02±0.04
F3	3.77 ± 0.11	0.42±0.01	898±0.97	6.42±0.01	98.60±0.02
F4	3.36 ± 0.10	0.23±0.01	899±0.97	6.54±0.02	99.12± 0.01
F5	3.15 ± 0.05	0.44±0.01	899±0.97	6.52±0.02	96.04±0.08
F6	3.68 ± 0.05	0.32±0.01	897±0.85	6.51±0.01	88.02±0.09
F7	3.23 ± 0.06	0.36±0.01	901±0.93	6.54±0.01	92.64±0.02
F8	3.23±0.12	0.44±0.01	900±0.93	6.52±0.02	93.05±0.06
F9	3.65±0.15	0.24±0.01	901±0.92	6.45±0.02	92.57±0.02

Table 6

All values are expressed as mean ±SD; *n=10, **n=6, ***n=20, #n=30 each value represents as singly. Where n = no of tablet.

In- Vitro Drug Release Study

The results obtained from the dissolution studies of various batches F1-F9 among these batches, the batch F4 showed 92.12% respectively cumulative drug release within 12 min.

Batch code / Time in min	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	25.78±0.04	20.91±0.06	28.70±0.07	27.24±0.11	19.45±0.09	22.37±0.01	24.32±0.05	28.70±0.09	22.86±0.07
4	37.74±0.09	31.36±0.08	40.69±0.06	37.76±0.03	32.24±0.07	36.24±0.03	36.27±0.04	38.26±0.04	39.65±0.16
6	45.94±0.06	42.90±0.12	53.30±0.11	55.69±0.04	47.76±0.09	44.93±0.08	48.42±0.08	47.92±0.08	52.25±0.07

8	61.52±0.04	55.53±0.11	68.48±0.13	68.46±0.02	62.4±0.06	59.51±0.09	62.51±0.11	63.04±0.07	63.04±0.05
10	72.90±0.11	64.53±0.09	74.28±0.09	79.58±0.02	76.75±0.13	73.92±0.02	80.71±0.12	78.27±0.15	74.19±0.09
12	89.02±0.06	79.06±0.06	81.18±0.04	92.12±0.06	84.42±0.12	89.63±0.03	93.16±0.09	87.02±0.12	87.39±0.13

Table 7: In-vitro dissolution study.

The graphical representations of dissolution study of all batches were represented in Fig. 7 and Table 6. Thus the dissolution study suggested that maximum Atenolol was released within 12 min in phosphate buffer 6.8.

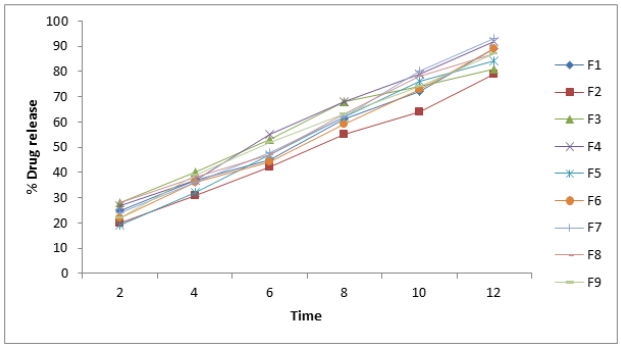

Figure 7: Graphical representations of in- vitro dissolution study of all Batches.

Stability Study: (ICH Guideline Q1 R2)

The effect of temperature and humidity was determined at 40ºC ±0.5ºC/75% ± 5%RH maintained in environmental stability chamber for one month. Evaluation was done after 30 days. Results are represented in TABLE 7.

Parameters	Results obtained at 0 days	Results obtained after 30 days
Appearance	Smooth	Smooth
Hardness (kg/cm2)	3.36 ± 0.10	3.34±0.08
Friability (%)	0.23 ± 0.01	0.22±0.01
Weight variation (mg)	899 ± 0.97	897±0.86
Drug content (%)± SD	99.60 ± 0.02	98.32±0.76
In-vitro drug release± SD	92.12±0.06	90.20±0.16

Table 8: Effect of Temperature and Humidity on Optimized Batch after Stability.

CONCLUSION

Thus, it was concluded that it was possible to formulate medicated chewing gums of antihypertensive drugs such as Atenolol. 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 & Stability.

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