Available online on 15.04.2024 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Research Article

Formulation Development of Medicated Chewing Gum by Direct Compression utilizing the SeDeM Diagram Expert System

Preeti Gajendra Karade *, Sonal Jadhav (Mali), Rohit Ramesh Shah

Department of Pharmaceutics, Appasaheb Birnale College of Pharmacy, Sangli, Maharashtra, India

Article Info:

Article History:

Received 03 Feb 2024
Reviewed 07 March 2024
Accepted 26 March 2024
Published 15 April 2024

Cite this article as:

Karade PG, Jadhav (Mali) S, Shah RM, Formulation Development of Medicated Chewing Gum by Direct Compression utilizing the SeDeM Diagram Expert System, Journal of Drug Delivery and Therapeutics. 2024; 14(4):59-68

DOI: http://dx.doi.org/10.22270/jddt.v14i4.6545

*Address for Correspondence:

Preeti Gajendra Karade, Department of Pharmaceutics, Appasaheb Birnale College of Pharmacy, Sangli, Maharashtra, India

Abstract

The main objective of this study was to prepare and characterize the MCG of Ondan HCl which helps to improve the effectivity of the drug and to investigate the applicability of the SeDeM system for the formulation of MCG. The Ondan HCl was formulated into directly compressed MCG utilizing the SeDeM Diagram Expert System. The MCG was optimized using 3^2 factorial design. Performance evaluation was carried out by evaluating different parameters. Statistical analysis showed that micromeritic properties were improved after inclusion of appropriate excipient in optimum amount. In-vitro drug release study showed 90.01% drug release whereas ex vivo buccal permeation study exhibited significant drug permeation within 15 min indicating its potential for increasing bioavailability. It was concluded that various characteristics of powder material at pre formulation level can be successfully predicted by SeDeM diagram expert system. The developed medicated chewing gum is more effective than mouth dissolving and conventional tablet formulation.

Keywords: Ondansetron HCl; Medicated chewing gum; direct compression; SeDeM diagram expert system.

INTRODUCTION

Medicated chewing gum (MCG) a cohesive confectionery product rich in bioactive substances is chewed to release the drug. They are highly accepted by children and teenagers for their joyful use.[1] According to the European Pharmacopoeia and guidelines for pharmaceutical dosage forms issued in 1991 by the Committee for Medicinal Products for Human Use (CPMP) MCG are defined as, "solid single-dose preparations with a base consisting mainly of gums that are intended to be chewed but not swallowed, providing a slow steady release of the medicine contained".[2] During the process of chewing, the drug contained in the MCG is released into saliva. Due to its large vascularisation it can be absorbed by oral mucosa or swallowed into stomach and absorbed from gastrointestinal tract.[3] MCG are used for delivering drugs in the buccal mucosa to achieve a local or systemic effect.[4] It can also be administered anywhere and at any time as it does not require any liquids to aid swallowing.[5] Drugs absorbed through 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.[6]

The SeDeM expert system is useful tool, which provides information about the suitability of making tablets by direct compression. This methodology can be applied to elucidate the physical profile of API and excipients used to formulate drugs by direct compression technology.[7] In addition to formulation of directly compressible tablet, the SeDeM diagram expert system is also used and adapted to other solid oral dosage forms, prepared by direct compression.[8-11]

Antiemetics are used for prevention or suppression of vomiting. They act by blocking several receptors located in vomiting centres such as H_1 histaminic, dopamine D_2, 5-HT_3 receptor, muscarinic, and neurokinin1 (NK_1) receptor. Drugs such as H_1-antihistamines, Anticholinergics, Neuroleptics, 5-HT_3 antagonists act by penetrating blood brain barrier which leads to sedation. 5-HT_3 antagonists such as Ondan HCL and Granisetron act as 5-HT_3 blockers. It blocks emetogenic impulses at both their peripheral origin and central relay.[12] Ondan HCL is the drug of choice to prevent nausea and vomiting that may cause due to chemotherapy, radiation therapy, and post-operative conditions in cancer and cytotoxic agents. Ondan HCL has low oral bioavailability due to its extensive metabolism in liver.[12] It is available in the form of oral tablets, orally disintegrating tablets, suspensions and injections. But these formulations have several disadvantages such as difficulty in swallowing tablets which also requires water. Besides these, suspension does not have pleasant taste and dose accuracy. Also, patients suffering from trypanophobia experience difficulty in medication injection by needle.[13] The purpose of this study was to prepare and characterize the MCG of Ondan HCL which helps to improve the effectivity of the drug and also to investigate the applicability of the SeDeM system for the formulation of MCG by direct compression method.

MATERIALS AND METHODS

Materials

Ondan HCL was received as gift sample from CTX Life Sciences Pvt. Ltd. (Surat, Gujarat). HIG-04 was received as gift sample from Cafosa (Barcelona, Spain). All other ingredients and solvents used were of analytical grade.

Drug excipients compatibility study

Fourier Transform Infrared Study (FTIR)

The drug-excipient compatibility study was carried out by FTIR (Jasco FT-IR 4100). FTIR spectra of the pure drug, gum base, and mixture of drug-excipients were recorded. Spectra were recorded in the wavelength region of 4000-400 cm^{-1}. The peaks were observed for any types of interaction between the drug and excipients.[13]

Preformulation study of powder blend

Powder evaluation as per SeDeM diagram expert system:

Based on the concept of Quality by Design (ICH Q8) the SeDeM diagram expert system evaluates critical quality attributes that have an impact on the quality of the final product. The SeDeM diagram expert system provides the profile of excipients and drug in powder form with respect to their suitability for direct compression. This profile indicates whether a powder can successfully be compressed by direct compression technology or whether it needs to be adjusted with appropriate additional excipients. Evaluation of the Ondan HCl powder, Health in Gum-04 (HIG-04), and MCG formulations (with and without additional excipients) were determined according to the SeDeM diagram expert system to establish their appropriateness for direct compression. By using the pharmacopoeias whenever possible, twelve parameters were determined in triplicate.[14] Also results obtained from the parameters are processed using the equations presented in (Table 1). All data were captured using Microsoft Excel™ 2010 for windows™.

Dimensional parameter

Bulk density (Da) and tapped density (Dc) was calculated according to method described in Section 2.9.34 of the European Pharmacopeia.[15]

Compressibility parameter

To represent the compressibility factor Cohesion index (Icd), carr's index (IC) and inter-particle porosity (Ie) parameters were grouped together.

These affect the size of the tablet and its capacity to pile up. In addition, these tests are used in the calculus of other mathematical indexes for the determination of the compression parameter. These affect the compressibility of the powder.Thus, the following equations were applied:

$$Ie = \frac{(Dc-Da)}{Dc} \times Da \qquad \text{Eq-1}$$

$$IC = \frac{(Dc-Da)}{Dc} \times 100 \qquad \text{Eq-2}$$

The cohesion index was experimentally determined by directly compressing a powder sample on a tablet press. The hardness (N) of the obtained tablets from each powder sample was noted and the mean values calculated. The SeDeM diagram expert system suggests that if a powder mixture cannot be tableted, lubricant should be added.[16]

Flowability/powder Flow parameter

Flowability/powder flow parameters includes the Hausner's ratio (IH), angle of repose (α), and powder flow (t") parameters[16]. The IH was calculated from Da and Dc employing the following equation:

$$IH = \frac{Dc}{Da} \qquad \text{Eq-3}$$

Angle of repose was calculated where the fixed-height method was applied testing a 100 gm powder sample. The subsequent equation was employed, utilizing the radius (r) and height (h) of the cone formed to calculate the angle of repose (α).

$$\tan \alpha = \frac{h}{r} \qquad \text{Eq-4}$$

Powder flow (t"), expressed in seconds and tenths of a second per 100 gm sample, in accordance with the BP. These parameters influence the flowability of the powdered substance when compressed.

Lubricity/stability parameter

Loss on drying (%HR) was determined using the method described in 2.2.32 of the European Pharmacopoeia.[17] Powder sample (1 gm) was dried in an oven at 105°C ± 2°C until a constant weight was obtained. To determine hygroscopicity (%H), (1 gm) powder sample was stored in a stability test chamber (Tempo) set at 76% (± 2%) relative humidity and a temperature of 22°C (± 2°C) for 24 h, where change in weight was noted.%HR and %H have an effect on the lubricity and stability of formulation.

Lubricity/dosage parameter

Particle size analyses of the powder samples were conducted by means of laser diffraction equipped with a Hydro 2000 SM dispersion unit. The percentage particles measuring smaller than 50 µm (%Pf) were consequently auto-calculated. Homogeneity index (Iθ) was calculated according to the General method 2.9.12 of the European Pharmacopeia.[18]

Determination of acceptable limit values

Radius values (r) were calculated from numeric values of each SeDeM diagram parameter which were plotted on a polygon diagram. Based on the SeDeM diagram expert system following indices were calculated.

Parameter index (IP)

$$\text{Parameter index(IP)} = \frac{(\text{No.p} \geq 5)}{(\text{No. Pt})} \qquad \text{Eq-5}$$

Where No.p≥ 5 represents the parameters with values equal to, or more than 5 and No.pt represents the total number of parameters. Acceptability limit relates to a score of 5 or higher.

Parameter profile index (IPP)

$$\text{Parameter profile index(IPP)} = \text{mean r} \geq 5 \text{ of all parameters} \qquad \text{Eq-6}$$

Where mean r represents the mean value of the parameters. The acceptable limit corresponds to a score of 5 or higher.

Good compressibility index (IGC)

$$\text{Good compressibility index (IGC)} = IPP \times f \qquad \text{Eq-7}$$

Where f is the reliability factor and was calculated as follows:

$$f = \frac{\text{Polygon area}}{\text{Circle area}} \qquad \text{Eq-8}$$

- For infinite number of parameters, f = 1 (max. value)
- For 15 parameters, f = 0.971;
- For 12 parameters, f = 0.952
- For 08 parameters, f = 0.900

The acceptability limit was calculated by formula

$$IGC = IPP \times f > 5 \quad \text{Eq-9}$$

Powders with an IPP and IGC below 3 are not suitable for direct compression, values from 3 to 5 suggest the use of excipients to improve deficient powder properties and values above 5 indicate suitable characteristics for direct compression.[19]

Calculating the amount of excipients required to adjust a deficient parameter

After characterization of the API, gum base and formulation 1by the SeDeM expert system, it was noted that factor Compressibility and flowability (two indexes below 5) needs to be improved, therefore an individual mathematical analysis was performed to determine the percentage of excipient required in order to obtain tablets by DC. In order to select the most effective excipient, as well as the lowest possible concentration required to correct the compressibility deficiencies, the following equation that considers a minimum radius value of >5 can be applied.

$$CP = 100 - \left[\frac{(RE-R)}{(RE-RP)} \times 100\right] \quad \text{Eq-10}$$

Where,

CP- % corrective base (minimum amount to be added)

RE- mean incidence radius value (in this study: compressibility) of the corrective excipient

R- value of mean incidence radius to be obtained in the mixture

RP- value of mean incidence radius (compressibility) of the powder to be corrected.

Formulation of medicated chewing gum

Optimization using 3^2 factorial design

Ondansetron HCl chewing gum was formulated by using the 3^2 full factorial design. Gum base (X_1) and Talc (X_2) were selected as two independent variables at three levels. With the help of a mathematical model, the effect of these factors on crushing strength (Y_1) and % of drug release (Y_2) was studied.

Preparation of medicated chewing gum

Medicated chewing gums were prepared by DC technique. Ondansetron HCl (4 mg) and gum base powder were thoroughly blended in a mortar. Soy lecithin, orange oil, and aspartame were added to it. The lubricant and glidant were added after thorough mixing. Using flat-faced punches, the powder was compressed into tablets by using Fluidpack-Accura 10-station tablet press compression equipment.

Evaluation of medicated chewing gum

Physical characterization test

The colour of all the formulations was observed visually and reported. Thickness of chewing gum was measured using Digital vernier calliper (Aerospace).The investigation was done in triplicate.

Uniformity of weight

Twenty tablets were chosen at random and weighed one at a time using an electronic balance (Shimadzu). The weight of a tablet was calculated on average.[20, 21]

$$\text{Percentge weight variation} = \frac{(\text{weight of individual MCG})}{\text{Average weight of 20 MCGs}} \times 100 \quad \text{Eq-11}$$

Friability

Twenty MCGs were weighed and placed in the Roche Friabilator and revolved for four minutes at a speed of 25 rpm. The tablets were dusted &reweighed. The difference in weight was expressed in percentage and is specified to be less than 1%. The test was considered to be failed if damaged tablets were present.

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100 \quad \text{Eq-12}$$

Stickiness

The chewing gum was placed on a plain surface. A weight of 250 gm was hammered on it for a period of ten minutes. Hammering was at the frequency of about 30/min. After 10 min. sticking of the gum was observed manually.

Crushing strength

Tablets must be hard enough to remain intact when handled normally, but soft enough to be properly chewed in the mouth. The crushing strength was tested by using Monsanto tester (Coslab). The mean crushing strength of each formulation was determined in triplicate.

Uniformity of Content

Three chewing gums were crushed in mortar and powder equivalent to 10 mg of Ondan HCl was added in 100 ml of methanol. The absorbance measurements of these solutions were taken by UV-Visible spectrophotometer (Jasco V-750) at 246 nm.[13]

In-vitro drug release study

In-vitro drug release study was performed on modified I.P. disintegration test apparatus (Veego VTD-D) by using phosphate buffer of pH 6.8 solution. The apparatus applies mechanical force to the chewing gum by vertically moving the lower jaw combined with rotation of the upper jaw with agitation of the release medium. The parameters were set to 30 chews per minute for chewing frequency, 40° for the twisting angle, and 1.65mm for the jaw distance. The MCGs were placed in the chewing chamber between two nets and equilibrated for 15 min before starting the chewing for a total time of 20 min at 37 ± 0.5 °C. The sample was collected at a regular interval of 3 min for 15 min. The drug concentration was determined by UV spectroscopy.[22- 24]

Ex-vivo buccal permeation study

Goat buccal mucosa was obtained from the local slaughter house. Underlying fat and loose tissues were separated and then it was washed with isotonic phosphate buffer pH 6.8 at 37°C.

It was then placed between two compartments (donor and a receiver) of the Franz diffusion cell. Donor compartment was filled with phosphate buffer of pH 6.8 (salivary pH) while receiver compartment was filled with phosphate buffer of pH 7.4 (blood pH). The average amount of Ondan HCl released from optimized formulation after 15 min of chewing, was placed in the donor compartment. It was allowed to permeate through buccal mucosa for 30 min. At 5 min interval the sample was collected from the receiver compartment and analysed by the UV-spectrophotometer at 249 nm, to determine the drug content permeated through buccal mucosa.[25] Chi-square test was used to investigate "is there significant correlation between observed and expected value of % drug permeation or not".[13]

Differential Scanning Calorimetry (DSC)

Thermograms of pure Ondan HCl and optimized formulation (F5) were recorded using DSC (Model-SDT Q600, TA Instruments, USA) instrument.[20]

Scanning Electron Microscopy (SEM)

The morphology of f5 formulation (outer surfaces, and internal structures) were observed using SEM (JOEL JSM-6360, Japan).[13, 26]

Stability study of formulation

The chewing gums were covered in aluminium foil and were placed in amber colored glass container Remi Stability Chamber (Tempo), stored at $40^0C \pm 2^0C$ with the relative humidity of 75% RH ±5% RH (ICH Q1 (R2) Stability testing Guidelines). The samples were withdrawn after one month and evaluated for appearance, crushing strength, drug content, and cumulative % drug release.[20]

RESULT AND DISCUSSION

Compatibility study of drug with excipients

The spectrum of mixture is given in (Figure 1). The drug and gum base shows characteristics peaks which were present in IR spectra of physical mixture. According to the IR investigation, there was no sign of any kind of chemical interaction between the pure drug and the employed excipients.

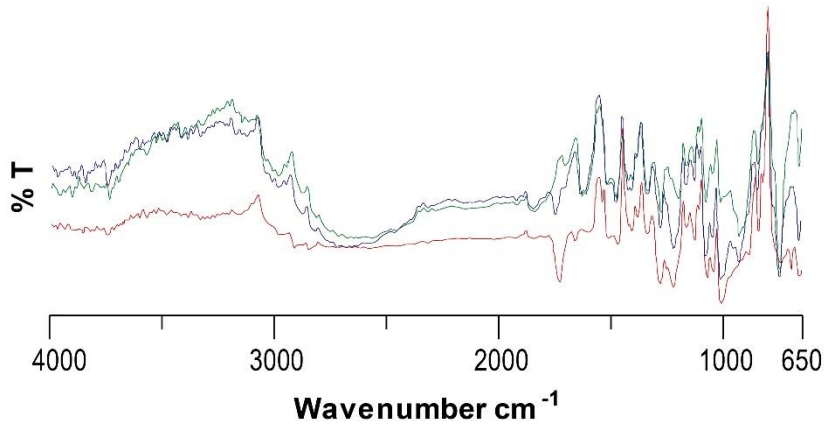

Figure 1: Overlay IR spectrum Gum base-a, Pure drug-b, Mixture-c

Preformulation study of powder blend

Preformulation study of powder was studied by using SeDeM diagram expert system.

SeDeM diagram results for the of Ondan HCL and DC excipients

The parameters were determined using the method described, and radius of each diagram was computed using the equations in (Table 1). The values obtained were then transformed into radii (r), as indicated in (Table 2) and (Table 3). Each parameter was measured three times. The results of the powder characteristics were displayed in a polygonal radar-chart and the values are converted into acceptability indices. The higher the r values of the tested parameters, larger the coloured area in the SeDeM diagram, and the more likely the powder is suitable for DC. The acceptance criterion of the IP, IPP and IGC were calculated. A powder with value of IPP and IGC below 3 is unsuitable for direct compression; values from 3 to 5 suggest the use of excipients to improve the deficient mixture properties and values above 5 indicate suitable characteristics for DC.

From (Table 2), it is interesting to note that although the bulk and tapped densities of Ondan HCl tested produced acceptable r-values, the inter-particle porosity and Carr's index calculated from the said density values are deemed unacceptable as it is well below the minimum standard value of 5. Moreover, the Ondan HCl is considered having a higher bulk density and inter particle porosity, and a less suitable flowability (in terms of Carr's index) compared to the HIG-04.

On the other hand, there were no clear variations between the inter-particle porosity, Carr's index values of the HIG-04. Although the Hausner ratio, powder flow parameters, as well as the flowability factor, adhere to the SeDeM diagram expert system, signifying acceptable powder flow for the Ondan HCl and HIG-04, the angle repose value of Ondan HCl was shown to be unacceptable which is below minimum standard value of 5.Compressibility factor values of HIG-04 and Ondan HCl were undeniable having unacceptable compressibility characteristics. From result, loss on drying value of Ondan HCl was found unacceptable as compared to HIG-04 which affect to stability factor. Hygroscopicity and lubricity/ stability values for all powder were found to be acceptable which predict increased flowability as well as directly compressibility.

After blending Ondan HCl with the HIG-04 and excipients to produce Formulation 1, the above-mentioned characteristics (flow and cohesion indexes) of Ondan HCl were indicated by a decrease of the r values of the Formulation 1 in the SeDeM-Diagram (Table 2**;** Figure 2). This is furthermore due to unacceptable Inter-particle porosity, Carr's index, Cohesion index and flow parameter obtained. The entire formulation acceptance indices decreased below the DC limit. Consequently, to apply DC to Ondan HCl formulation an excipient is required to enhance the compressibility factor. This excipient is identified by the SeDeM expert system.

Table 1: Parameters, equations, limits, and factors used in the SeDeM diagram expert system

Incidence	Parameter (Symbol)	Equation	Acceptable ranges	Conversion factor applied
Dimension	Bulk density (Da)	Da=m/Va	0-1 g/ml	10v
	Tapped density (Dc)	Dc=m/Vc	0-1 g/ml	10v
Compressibility	Inter-particle porosity (Ie)	Ie=(Dc-Da)/Dc*Da	0-1.2	10v/1.2
	Carr's index (IC)	IC=(Dc-Da)/Dc*100	0-50%	v/5
	Cohesion index (Icd)	Experimental	0-200 (N)	v/20
Flowability/powder flow	Hausner's ratio (IH)	IH=Dc/Da	3-1	(30-10v)/2
	Angle of repose (α)	$\alpha=\tan^{-1}h/r$	50-0 (^{0})	10-(v/5)
	Powder flow (t")	Experimental	20-0 (s)	10-(v/2)
Lubricity/ stability	Loss on drying (%HR)	Experimental	10-0 (%)	10-v
	Hygroscopicity (%H)	Experimental	20-0 (%)	10-(v/2)
Lubricity/ dosage	Particles<50 µm (%Pf)	Experimental	50-0 (%)	10-(v/5)
	Homogeneity index (Iθ)	$I\theta=Fm/(100\mp\Delta Fmn^a)$	$0\text{-}2\times10^{-2}$	500v

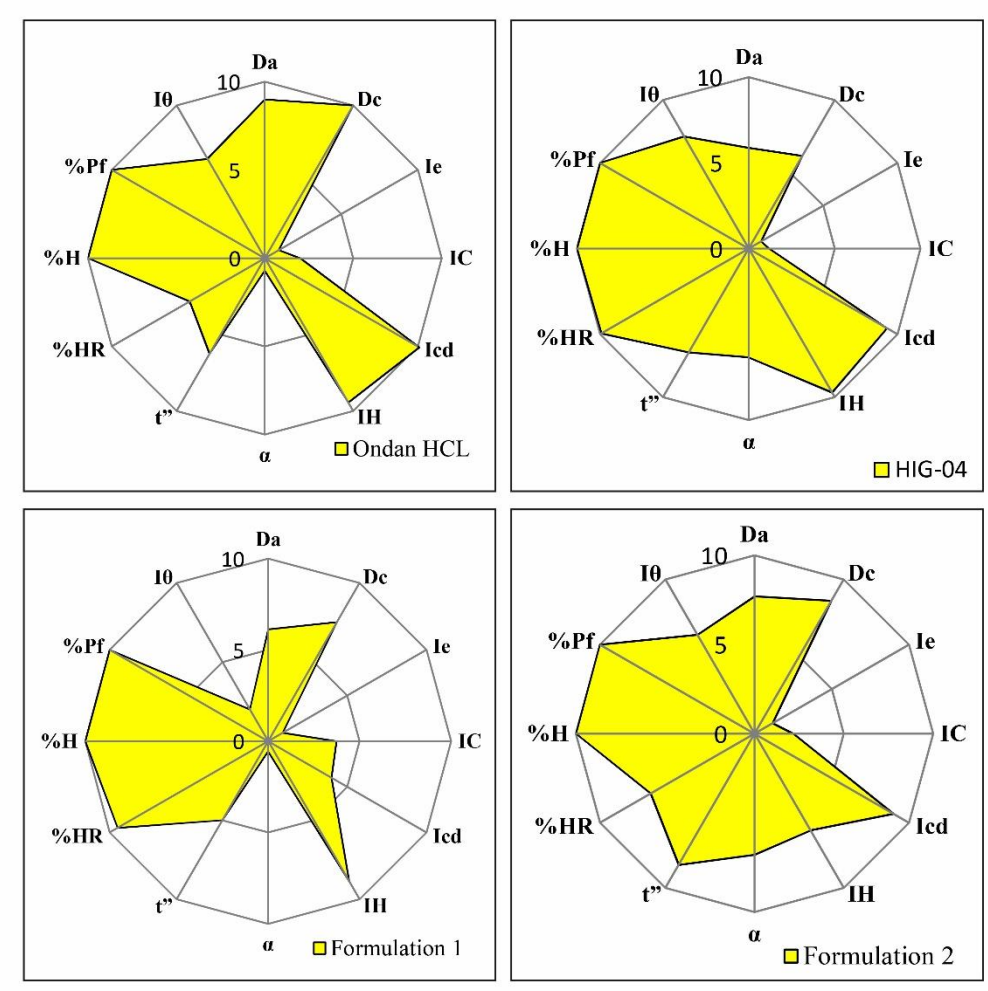

Figure 2: SeDeM diagram for Ondan HCl, HIG 04, Formulation 1 and Formulation 2

Table 2: Individuals radius parameters values of Ondan HCL, HIG-04 and formulations.

Excipient	Da (gm/ ml)	Dc (gm/ ml)	Ie	IC (%)	Icd (N)	IH	α (⁰)	t" (s)	%HR (%)	%H (%)	%Pf (%)	Iθ
Ondan HCL	9	10	**0.91**	**2**	10.1	9.45	**0.71**	6.25	**4.9**	10	10	6.50
HIG-04	5.88	6.25	**0.83**	**1.18**	9.3	9.7	6.35	7	9.9	10	10	7.55
Formulation 1	6.12	7.53	**0.91**	**3.74**	**4**	8.85	**0.56**	5	9.5	10	10	**2**
Formulation 2	7.70	8.60	**1.17**	**2.17**	9	6.27	6.80	8.50	6.71	10	10	6.40

Values indicated in bold are considered unacceptable according to the limits set by SeDeM diagram expert system; Formulation 1 is without lubricant, Formulation 2 is with lubricant.

Table 3: Mean incidence and parametric index values of Ondan HCL, HIG-04, and formulations.

Formulations	Dimension	Compressibility	Flowability	Lubricity/ stability	Lubricity/ dosage	IP	IPP	IGC
Ondan HCL	9.5	**4.33**	7.45	9.65	8.25	0.66	8.91	8.48
HIG-04	6.06	**3.77**	7.83	9.95	8.77	0.83	8.19	7.79
Formulation 1	6.83	**1.55**	**4.80**	9.75	5	0.75	5.18	**4.13**
Formulation 2	8.15	5.11	7.19	5.04	8.2	0.80	8.15	7.78

Values indicated in bold are considered unacceptable according to the limits set by the SeDeM diagram expert system

Selection of most suitable directly compressible (DC) lubricant for the compression of MCG

A study of SeDeM diagram for Formulation 1 (Table 3) indicate that is a formulation with insufficient compressibility properties (mean incidence radius = 1.55) and limited rheological properties (mean incidence radius is= 4.80). In order to formulate suitable blend for DC with Ondan HCl, a lubricant must be used which, when used in the smallest possible quantity, improves the poor SeDeM parameters. The parameters of three excipients were obtained (Table 4) in accordance with the described methodology and were converted to diagram radius (Figure 3; Table 5) by applying the equations proposed by Sune and colleagues.[7]

Table 4: Radius values of parameters for DC excipients

Excipient	Da (gm/ml)	Dc (gm/ml)	Ie	IC (%)	Icd (N)	IH	α (⁰)	t" (s)	%HR (%)	%H (%)	%Pf (%)	Iθ
Aerosil 200 Pharma	3.47	4.63	6.02	5.01	2.2	5.55	3.46	10	3.84	8.17	3.38	5
Mg. stearate	2.48	3.73	10	6.70	3	4.99	4.13	5.50	3.46	3.17	3.60	4.9
Avicel PH-101	5.58	8.46	5.08	6.81	4	4.95	3.51	1.90	0.00	8.12	3.25	6

Table 5: Mean incidence values and parametric index for DC excipients

Excipient	Dimension	Compressibility	Flowability	Lubricity/ stability	Lubricity/ dosage	IP	IPP	IGC
Aerosil 200 Pharma	4.05	7.01	3.01	6.01	6.69	0.67	5.29	5.04
Mg. stearate	3.11	8.90	3.04	3.32	4.65	0.33	4.83	4.60
Avicel PH-101	7.02	7.30	4.98	4.06	2.75	0.58	5.38	5.12

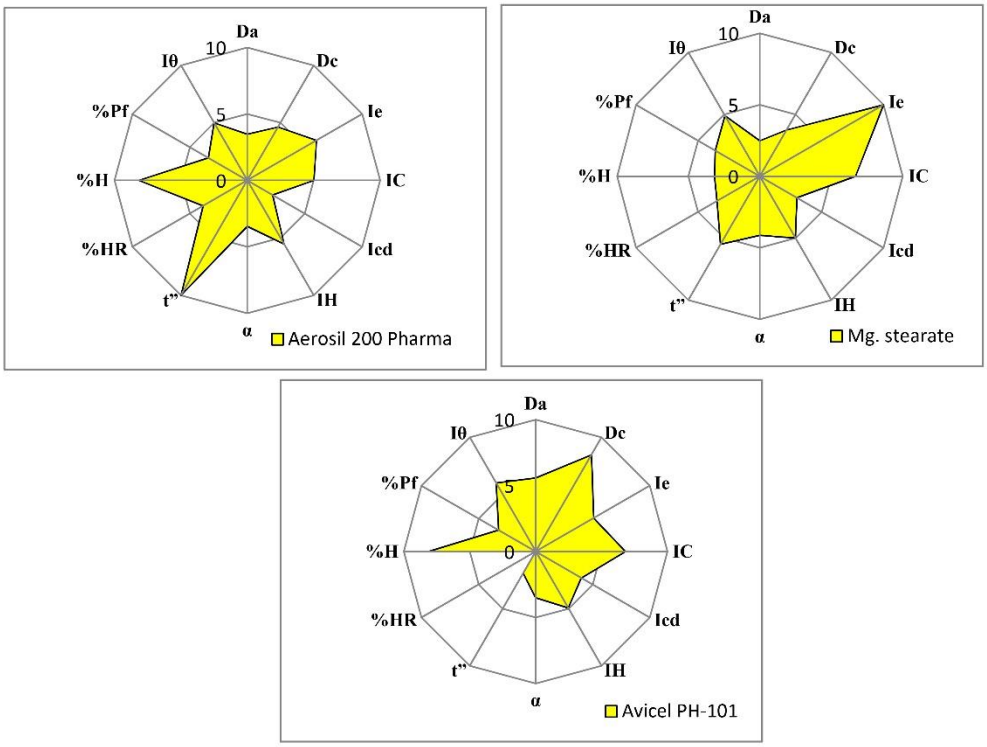

Figure 3: SeDeM diagram for Aerosil 200 Pharma, and Mg. Stearate and Avicel PH-101.

We used the numerical equation of the SeDeM expert system t o select excipients and concentrations to correct for deficienci es, particularly compressibility (Eq-10). The equation was specifically designed for this purpose and was intended for use in calculating the amount of lubricant required to compress formulation. Once the unknown values in Eq-10 have been replaced with the calculated values required for each substance in order to obtain R=5 (5 is minimum value that is necessary in order to achieve good compression), the result shown in (Table 6) are obtained. It was observed that the incidence value R=5 was reached with the lowest level concentration of magnesium stearate among the preselected group of excipients. So magnesium stearate is most suitable excipient to correct the deficit (compressibility) with the lowest concentration (29.09 %). According to the SeDeM diagram expert system, the addition of Mg. stearate greatly enhanced the flowability of the MCG formulations into the tablet die, which led to the manufacture of more repeatable MCG units when considering weight. Mg. stearate serves as both a lubricant and glidant, which increases not only the flowability, but it also lowers cohesion to tablet punches. This is possibly due to the ability of magnesium stearate to reduce inter-particle forces and improve particle flow into openings between other particles during compression.

Table 6: Amount of excipient required in order to ensure that formulation mixture will give a compressibility mean incidence of 5

Excipient	Aerosil 200 Pharma	Mg. stearate	Avicel PH-101
No.	**1**	**2**	**3**
RE	7.01	8.90	7.30
RP	3.40	3.40	3.40
R	5.00	5.00	5.00
% excipient (CP)	44.32	29.09	41.03

Characterization of MCG formulation as per SeDeM diagram expert system

The MCG formulation 2 was evaluated by the SeDeM diagram expert system and the results obtained were used to calculate the parameter, factor, and index values from which SeDeM diagrams were subsequently constructed (Figure 2). Generally, inclusion of Ondan HCL and HIG-04 into MCG formulations affected the parameter and factor values negatively, especially the compressibility factor, which is noticeable in (Table 2) and (Table 3) where Formulation 1 does not adhere to the set criteria. Additionally, the inter-particle porosity and cohesion index parameters found were inadequate. On the other hand, compressibility values for formulation 2(with the lubricant) showed acceptable results.

The flowability factor (Hausner ratio, angle of repose and powder flow) of Formulation 2 compared with, Formulation 1 is notably improved. It is also clear that, as compared to powder mixtures without a lubricant, the addition of Mg. stearate improved the majority of parameter and factor values. From (Table 3), furthermore, it is evident that according to the index values, although the parameter index value of Formulation 1 and Formulation 2 were deliberated satisfactory, Formulation 1 was not suitable for DC as compared to Formulation 2 because the good compressibility index values were not within the range of 5–10.Thus, from the results it was indicated that Formulation 2 showed excellent flow property and compressibility which is favourable for direct compression.

The aforementioned findings indicate that the SeDeM-System is sensitive for formulation changes of direct compressible chewing gum and imply the suitability of the SeDeM-System for prediction of direct compressibility. The results for improved compressibility and the improved flowability factor are given in (Table 3).

Evaluation of MCG tablet

The amount of gum base (X_1) and Talc (X_2) were selected as independent variables and the dependent variables were crushing strength and % drug release (%DR) at 15 min. The

data obtained was treated using Stat-Ease Design Expert 9.0.3.0 software and analysed statistically using analysis of variance (ANOVA).

Physical characterization of Chewing gum of Ondan HCl

The colour of all the formulations was observed to be off white. All the chewing gum tablet formulations passed the weight-variation test as per the I.P. specifications, and none of the chewing gum tablet was found to deviate from the mean weight of the tablets. Thicknesses of the tablets were observed to be in between 3.7 and 4.2 mm. All the formulations were non-sticky. Friability was observed to be less than 1% which indicates the strength of tablets and also exhibit that these tablets can withstand the shocks during shipping, transportation and handling. Crushing strength is increased by decreasing amount of gun base and talc and vice versa (Figure 4). The Quadratic equation generated from the regression analysis for response variable X_1 and X_2.

Y_1 (kg/m^2) = +3.33-0.22*X_1-0.100*X_2-0.18* X_1 X_2-0.050* X_1^2+0.30 X_2^2 Eq-13

The values for these parameters are given in (Table 7).

Table 7: Evaluation of Ondan HCl Chewing gum tablet

Batch Code	Gum base	Talc	Weight uniformity* (%)	Friability* (%)	Thickness* (mm)	Crushing strength* (Kg/m^2)	Uniformity Content* (%)
F1	440	20	1.12±0.2	0.81±0.06	4.1±0.1	3.7±0.05	94.50±0.31
F2	450	20	1.78±0.1	0.71±0.07	3.7±0.1	3.8±0.05	98.05±0.32
F3	460	20	2.10±0.15	0.80±0.02	4.2±0.1	3.6±0.1	95.85±0.54
F4	440	40	1.02±0.2	0.76±0.09	4±0.15	3.5±0.2	97.56±0.38
F5	450	40	1.89±0.1	0.81±0.03	3.8±0.15	3.3±0.15	99.04±0.62
F6	460	40	2.03±0.2	0.83±0.05	4±0.15	3.1±0.20	97.99±0.30
F7	440	60	1.42±0.15	0.78±0.09	3.9±0.1	3.9±0.15	97.85±0.35
F8	450	60	2.12±0.15	0.70±0.09	4.2±0.15	3.5±0.15	98.88±0.22
F9	460	60	1.22±0.2	0.84±0.04	4.1±0.15	3.1±0.1	96.33±0.45

*Mean ± SD (n=3), * (n=20)

Uniformity of Content

Drug content was observed for all the formulations (94.50 ± 0.31% to 99.04 ± 0.62%), thus, all the formulations complied the uniformity of active content test. The values for uniformity of active content are given in (Table 7).

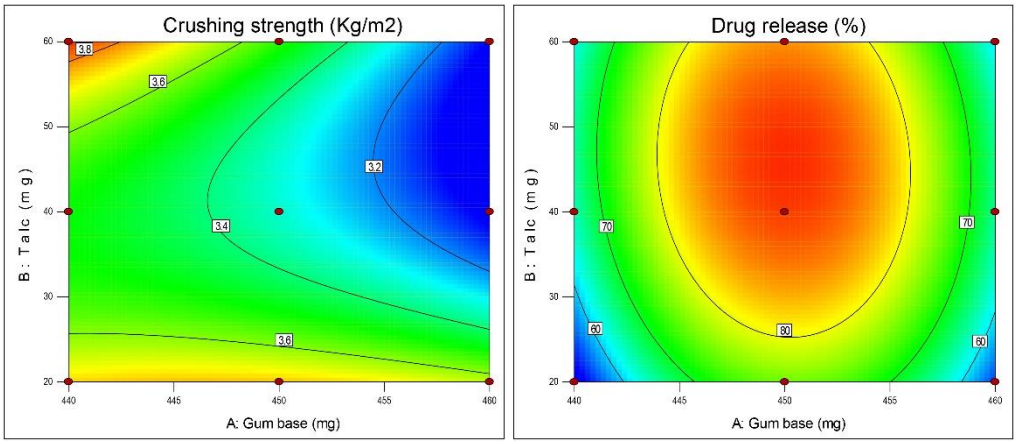

Figure 4: Contour plot for Crushing strength and % DR at 15 min.

In-vitro release test

The prepared formulations were analyzed for % drug release by using modified chewing apparatus. Formulation F5 showed highest drug release of 90.01%, whereas F1formulation showed the lowest drug release of 71.42% after 15 minutes (Figure 5). In 15 minutes, more than 70% of the drug was released from all formulations.In-vitro drug release values ranged from 71.42-90.01% in 15 minutes for F1-F9 formulations. Percent drug release after 15 minutes increases with increasing amount of gum base and talc. The Quadratic equation generated from the regression analysis for response variable X_1 and X_2

Y_2 (%) = +87.82+0.22*X_1+4.62*X_2-1.52* X_1 X_2-23.42* X_1^2-8.17* X_2^2 Eq-14

Graphical presentation of the data helped to show the relation between the response and the independent variables. The information given by graph was similar to that of mathematical equation obtained from statistical analyses (Figure 4).

Ex-vivo buccal permeation study

Results of the applied Chi-square test are mentioned in (Table 8). From the results, it was observed that the average amount of drug permeated through buccal mucosa was 36.67 ± 5.202%. Results of the Chi-square test suggested that there was a significant agreement between observed values and expected values (40.00%) with a high level of significance (P = 0.05). It is hypothesized from the results of the buccal permeation that the significant amount of the drug may permeated (absorbed) through the buccal route, which may increase bioavailability of Ondan HCl and decrease onset time.

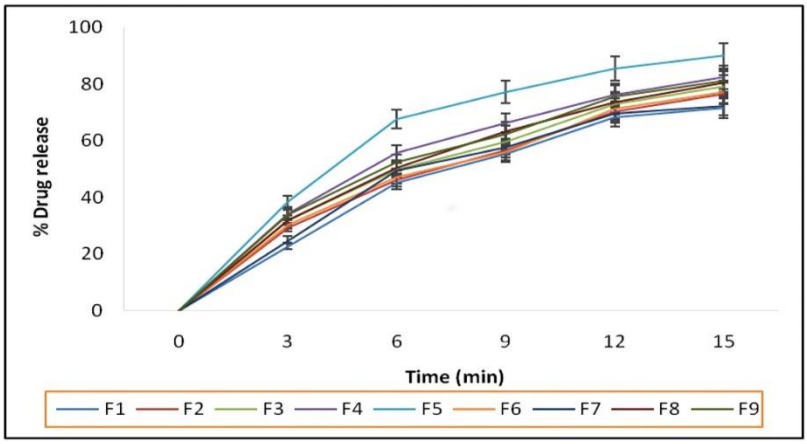

Figure 5: Comparative %DR profile of formulations F1-F9.

Table 8: Results of applied Chi-square test for ex-vivo buccal permeation study

Sample no.	Observed % permeation (O)	Expected % permeation (E)	$Chi_{cal}=\sum(O-E)^2/E$
1	36.6	40.0	0.289
2	40.8	40.0	0.020
3	29.6	40.0	2.651
4	37.8	40.0	0.110
5	31.6	40.0	1.721
6	43.1	40.0	0.255

Results: $Chi_{cal}=\sum(O-E)^2/E = 5.05$; $Chi_{tab} = 11.07$. So, $Chi_{cal}<Chi_{tab}$. Therefore, experimental values are in significant agreement with expected values.

Differential Scanning Calorimetry (DSC) study

The melting of Ondan HCl peak has been shifted towards 191.30^{0}C which is close its melting point. The optimized formulation F5 showed exothermic peak at 191.30^{0}C which is close to drug melting point. 332.30^{0}C indicates endothermic pick of Mg. stearate. Thus, concluded that a drug & formulation mixture does not form a complex but acts as physical mixture (Figure 6).

Scanning electron microscopy study

Scanning electron microscopy (SEM) image of optimized MCG formulation F5 was taken at 130X and 1000X magnifications. The SEM images clearly indicated optimal formulation with smoother surface. A MCG formulation with Mg. stearate seems to possess a smoother outer surface. At the higher-magnification images, it seems that this formulation produced MCG units with increased particle binding due to higher degree of plastic deformation.So it was concluded that there was more plastic deformation that may increases patient compliance due to its aesthetic surface property. In this way, the information provided by the SeDeM expert system allows the formulator to start working with excipients that have a high probability of providing a suitable formulation, thus reducing the lead time of the formulation (Data not shown).

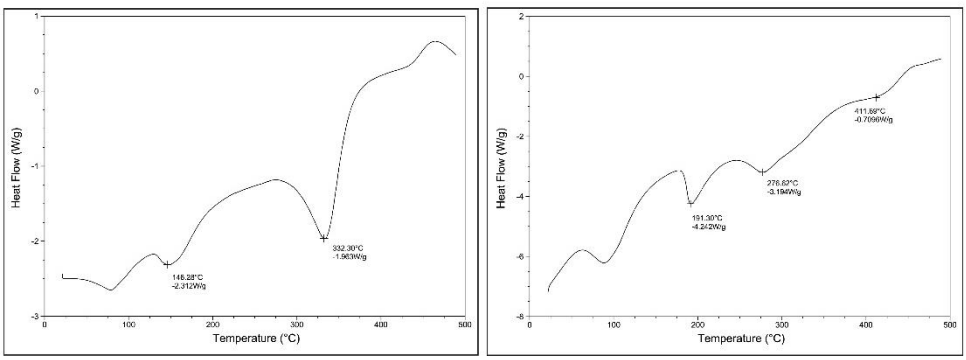

Figure 6: DSC Thermogram of Ondan HCl and optimized F5 formulation.

Stability study of optimized batch

During the stability studies no change in colour was found and chewing gum tablets were non sticky. From results it was observed that crushing strength of F5 was found to be reduced from 3.3 to 3.2Kg/m^2, which was within acceptable range. Drug content as well as %DR did not get much affected and reduced from 99% to 98.4%and 90% to 89.26% respectively.

CONCLUSION

In this study, the SeDeM diagram expert system was successfully applied for development and optimization of MCG formulations. The powders used for tablet compression was evaluated for pre-compression tests utilizing SeDeM diagram expert system to reduce both the number of experiments and time required to produce formulation. The study concludes the possibility of the formulation of the directly compressible MCG of Ondan HCl using Health in Gum (gum base) with the improved taste by using artificial sweetener. The first pass metabolism associated with Ondan HCl can also be solved by the MCG, as the main site of absorption is buccal. The MCG formulation of Ondan HCl is a novel approach for the treatment of nausea and vomiting. MCG can increase patient compliance and patient acceptance as well as increase the bioavailability of Ondan HCl as it showed significantpermeation through buccal mucosa. However, clinical pharmacokinetic data are needed to prove it further.

REFERENCES

1. Pathan AK, Panse G, Mishra A. Formulation and evaluation of ondansetron HCL chewing gum by compression method. Int J Recent Trend Sci Tech. 2018; 484-487.

2. European Pharmacopoeia, Directorate for the quality of medicines council of Europe. 2010; 1:709.

3. Shete RB, Muniswamy VJ, Pandit AP, Khandelwal KR. Formulation of eco-friendly medicated chewing gum to prevent motion sickness. Am Association Pharma Sci Pharm Sci Tech. 2015; 16:1041-50. https://doi.org/10.1208/s12249-015-0296-y PMid:25652732 PMCid:PMC4674635

4. Viljoen JM, Walts SV, Hamman JH. Formulation of medicated chewing gum containing Sceletium tortuosum and process optimization utilizing the SeDeM diagram expert system. Am Association Pharm Sci Pharm Sci Tech. 2021; 22: 102. https://doi.org/10.1208/s12249-021-01961-8 PMid:33712901

5. Chaudhary S, Shahiwala A. Directly compressible medicated chewing gum formulation for quick relief from common cold. Int J Pharm Invest. 2012; 2: 123-133. https://doi.org/10.4103/2230-973X.104395 PMid:23373003 PMCid:PMC3555007

6. Yadav S, Atram S, Bobade N. Development and evaluation of medicated chewing gum containing ondansetron hydrochloride. EU J Biomed Pharm Sci. 2021; 8:293-297.

7. Sune-Negre JM, Carreras MR, García RF, Garcia E. SeDeM Diagram: an expert system for preformation, characterization and optimization of tablets obtained by direct compression. Formulation tools for pharm dev. 2013; 109-135. https://doi.org/10.1533/9781908818508.109

8. Sipos E, Oltean AR, Szabó ZI, Rédai EM, Nagy GD. Application of SeDeM expert systems in preformulation studies of pediatric ibuprofen ODT tablets. Acta Pharm. 2017; 67: 237-246. https://doi.org/10.1515/acph-2017-0017 PMid:28590910

9. Aguilar-Díaz JE, García-Montoya E, Pérez-Lozano P, Suñe-Negre JM, Miñarro, M, Ticó JR. Predicting orally disintegrating tablets formulations of ibuprophen tablets: an application of the new SeDeM-ODT expert system. EU J Pharm Biopharm. 2012; 80:638-648. https://doi.org/10.1016/j.ejpb.2011.12.012 PMid:22245156

10. Aguilar-Díaz JE, García-Montoya E, Pérez-Lozano P, Suñe-Negre JM, Miñarro, M, Ticó JR. The use of the SeDeM Diagram expert system to determine the suitability of diluents-disintegrants for direct compression and their use in formulation of ODT. EU J Pharm Biopharm. 2009; 73:414-423. https://doi.org/10.1016/j.ejpb.2009.07.001 PMid:19602435

11. Khan A, Iqbal Z, Rehman Z, Nasir F, Khan A, Ismail M, Roohullah Mohammad A. Application of SeDeM Expert system in formulation development of effervescent tablets by direct compression. Saudi Pharm J. 2014; 22: 433-444. https://doi.org/10.1016/j.jsps.2013.07.002 PMid:25473332 PMCid:PMC4246396

12. Tripathi KD. Essentials of medical pharmacology, sixth ed. Jaypee brothers medical publishers (P) LTD. 2008; 639-647. https://doi.org/10.5005/jp/books/10282_49

13. Paradkar M, Gajra B, Patel B. Formulation development and evaluation of medicated chewing gum of anti-emetic drug. Saudi Pharm J. 2016; 24: 153-164. https://doi.org/10.1016/j.jsps.2015.02.017 PMid:27013908 PMCid:PMC4792901

14. Zieschang L, Klein M, Jung N. Formulation development of medicated chewing gum tablets by direct compression using the SeDeM-Diagram-Expert-System. EU J Pharm Biopharm. 2019; 144: 68-78. https://doi.org/10.1016/j.ejpb.2019.09.003 PMid:31493511

15. Strasbourg FR. Bulk Density and Tapped Density of Powders. 2.9.34., in: European Pharmacopoeia, 9th ed., European Directorate for the Quality of Medicines, Council of Europe. 2016; 359-361.

16. SuñéNegre JM, García Montoya E, Pérez Lozano P, Aguilar Díaz JE, Roig Carreras M, Fuster García R, MiñarroCarmona M, Tico Grau JR. SeDeM Diagram: A New Expert System for the Formulation of Drugs in Solid Form, in: In Tech (Ed.), Expert Systems for Human, Materials and Automation. 2011. https://doi.org/10.5772/16540

17. European Pharmacopoeia, European Directorate for the Quality of Medicine & Health Care of the Council of Europe (EDQM), edn.2017; 9:3104-5.

18. Perez P, Sune-Negre JM, Minarro M, Roig M, Fuster R, Hernandez C, Ruhı R, Garcıa-Montoya E, Tico JR. A new expert system (SeDeM Diagram) for control batch powder formulation and preformulation drug products. EU J Pharm Biopharm. 2006; 64: 351-359. https://doi.org/10.1016/j.ejpb.2006.06.008 PMid:16949262

19. Dai S, Xu B, Shi G, Liu J, Zhang Z, Shi X, Qiao Y. SeDeM expert system for Directly compressed tablet formulation: a review and new perspectives. Powder Tech. 2019; 342:517-527. https://doi.org/10.1016/j.powtec.2018.10.027

20. Bagdane A, Thombre N. Formulation development and evaluation of atenolol based medicated chewing gum. Int J Drug Dev Res. 2021; 13: 1-8.

21. Indian Pharmacopoeia, Government of India ministry of Health and Family Welfare, Published by the controller of Publication, Delhi. 2007; 1815-1820.

22. Marzouk MA, Darwish MK, Abd El-Fattah MA. Development of medicated chewing gum of taste masked levocetirizine dihydrochloride using different gum bases: In vitro and in vivo evaluation. Drug Develop Ind Pharm. 2020; 46:395-402. https://doi.org/10.1080/03639045.2020.1724130 PMid:31996053

23. Jacobsen J, Christrup LL, Jensen N. Medicated chewing gum. Am J Drug Deliver.2004; 2:75-88. https://doi.org/10.2165/00137696-200402020-00001

24. Morjaria Y, Irwin WJ, Barnett PX, Chan RS, Conway BR. In vitro release of nicotine from chewing gum formulations. Disso Tech. 2004; 11:12-15. https://doi.org/10.14227/DT110204P12

25. Chaudhary SA, Shahiwala AF. Medicated chewing gum-a potential drug delivery system. Exp Opi Drug Deliv. 2010; 7: 871-885. https://doi.org/10.1517/17425247.2010.493554 PMid:20560779

26. Karade PG, Jadhav NR. Colon targeted curcumin microspheres laden with ascorbic acid for bioavailability enhancement. J Microencapsulation.2018; 35: 372-380. https://doi.org/10.1080/02652048.2018.1501111 PMid:30010458