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NOVEL FORMULATION DEVELOPMENT AND OPTIMIZATION OF MEDICATED CHEWING GUM OF ONDANSETRON HYDROCHLORIDE

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ABSTRACT

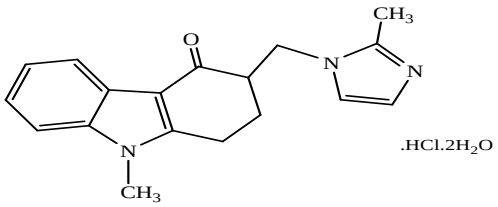
Medicated chewing gum is considered as vehicle or drug delivery system to administer active principles that can improve health and nutrition. It is a completely unique drug delivery system containing masticatory gum base with pharmacologically active ingredient and intended to use for local treatment of mouth diseases or systemic absorption through oral mucosa. The aim of present study was to prepare chewing gum of Ondansetron hydrochloride for the treatment of nausea and vomiting. Novel chewing formulation was prepared by using gum base as a base, Aerosil as a release modifier, sucrose as a filler and buffer. The effect of concentration of ingredients was studied. The dissolution studies showed that optimum amount of gum base shows superior results. Maximum peak plasma concentration is reached after approximately 1 h. This model is selected for the study in order to overcome the hepatic first-pass effect and there by possible reduction in the dose. To mask the bitter taste of Ondansetron hydrochloride, sodium saccharin was used as sugar base. Ondansetron hydrochloride has higher salivary (artificial saliva) solubility, less side effects and has short duration of action of about 3 hr; these factors make Ondansetron Hydrochloride a suitable candidate for formulation of medicated chewing gum used to treat nausea and vomiting.

KEYWORDS: Medicated Chewing Gum, Ondansetron, Nausea, Vomiting etc.

INTRODUCTION

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.[1] 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.[2] 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.[3]

Medicated chewing gums are defined by the Pharmacopoeia and therefore 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 drugs contained". According to European pharmacopeia, 2002 medicated chewing gum is meant to be chewed for a particular period of your time, required to deliver the dose, after which the remaining mass is discarded.[4] During the chewing process, the drug contained within the gum product is released from the mass in to saliva and it might 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.[5]



Ondansetron hydrochloride

9-methyl-3-((2-methyl-1*H*-imidazol-1-yl)methyl)-2,3-dihydro-1*H*-carbazol-4(9*H*)-one

Fig. 1: Structure and chemical name of Ondansetron hydrochloride.

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 variety of cognitive, recognition, and memory tests. The results provided the first evidence that the chewing of gum can improve episodic memory and working memory.[6]

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.[7]

The objective of this work is to formulate and develop medicated chewing gum delivery of Ondansetron hydrochloride for chemotherapy-induced nausea and vomiting, it's also planned to spot the important formulation parameters affecting the behavior of medicated chewing gum. The drug used in this work is a 5 HT_3 antagonist. 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.[8] Ondansetron hydrochloride 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. Ondansetron hydrochloride has a bitter taste so the formulations are repaired in order to mask the taste.[9]

MATERIALS AND METHODS

Materials: Ondansetron hydrochloride was supplied by Dr. Reddy's Laboratories, Hyderabad as a gift sample. All research grade excipients were procured from SD Fine Chemicals, Mumbai.

Methods

Taste masking of drug

Taste is one of important parameters in governing patient compliance. Ondansetron hydrochloride is an extremely bitter drug. Which is non palatable for oral administration by many patients. Therefore inclusion complexes of Ondansetron hydrochloride with sodium saccharin were prepared at three different molar ratio 1:1, 1:3, 1:5 by wetting the physical mixture of Ondansetron hydrochloride and sodium saccharin in a mortar & pestle with a minimum volume of water and kneaded thoroughly for at least 30 min to obtain a homogenous smooth paste, which was then dried in microwave oven and sieved through 22# sieve. The cavity size of Sodium Saccharin in aromatic ring moiety and physical forces and hydrophobic interactions stabilize the complex that is formed.[9]

Taste acceptability was measured by a taste panel of ten volunteers with Ondansetron Hydrochloride held in mouth for 10-25 sec, then spat out, and the bitterness level was recorded. Volunteers were asked to gargle with distilled water between drug & complex administration.

Table 1: Novel Formulation of Ondansetron hydrochloride medicated chewing gum.

Batch Code → / Ingredient (mg) ↓	A	B	C	D	E	F
Ondansetron HCl	04	04	04	-	-	-
Health in Gum	395	420	420	402	432	432
Aspartame	30	30	30	-	-	-
Drug + Sodium saccharin (1:3)	-	-	-	30	30	30
Mannitol	37	12	12	38	28	8
Aerosil	10	10	10	10	10	10
Magnesium Stearate	10	10	10	10	10	10
Talc	10	10	10	10	10	10

Formulation development and optimization

Preparation of medicated chewing gum

Ondansetron hydrochloride was used as an anti-emetic agent. Mixing of Gum base, Ondansetron hydrochloride, anti-adherent (Talc), after that the lubricant (Magnesium Stearate), and glidant (Aerosil) are mixed and lastly sweeteners were mixed. Screening of the mixed preparation through No. 22 sieve for reduces particles size. Sieving and blending (10 minutes) finally, the formulation was compressed using 12 mm punch in rotary tablet punching machine.

Determination of pre-compression characteristics[10,11]

Angle of repose: The frictional forces in loose powder can be measured by the angle of repose θ. This is the maximum angle possible between the surface of the pile of powder and the horizontal plane. The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the formed powder heap.

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

Bulk density = Weight of powder /Bulk volume…… (1)

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

Tapped density = Weight of powder/Tapped volume…… (2)

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

% compressibility index= 100*(1 – bulk density/tap density)…… (3)

Hausner's ratio: It is calculated from bulk density and tap density,

Hausner's ratio = Tapped density/Bulk density…… (4)

Determination of post-compression characteristics[12,13]

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

Friability: It is usually measured by the use of them Roche Friability tester (Kumar Mfg. Ltd.)10 tablets were randomly selected, weighed and were tested using the Roche Friability tester.

$(W_{initial}-W_{final})/W_{initial} \times 100$…… (5)

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

Drug content uniformity test: Ondansetron HCl chewing gum tablet from each batch was tested for their drug content. The chewing gum tablets were finely powdered and a quantity of powder equivalent to 10 mg of Ondansetron HCl were accurately weighed and transferred to 100 ml volumetric flasks containing 50 ml of methanol. The flasks were shaken to solubilize the drug. The volume was made up with methanol and mixed thoroughly. The solutions were filtered through membrane filter paper and analyzed for the content of Ondansetron HCl using UV spectrophotometer (Jasco-V630, Japan).

In vitro drug release studies

A specially developed chewing gum dissolution test apparatus was used for in vitro release testing of medicated chewing gums. Dissolution test of chewing gum tablets were performed using artificial saliva as dissolution medium. 2 ml test sample was withdrawn at particular time interval such as 2, 4, 6, 10, 12 min and replaced with fresh dissolution medium maintained at 37±1°C. The samples were filtered (membrane filter, 0.45µm) and analyzed using a UV spectrophotometer at λ_{max} 217 nm.

Estimation of chewing gum consistency

Chewing gum consistency was determined by chew out method. For estimation of chewing gum consistency the placebo chewing gums were prepared according to the formula, and they are given to the human volunteers to chew for certain time.

RESULTS AND DISCUSSION

Chewing gum formulation obtains fast/rapid onset of action, high bioavailability, pleasant taste, ease of administration without water, promotes higher patient compliance, reduce side effects, product distinctiveness from a marketing perspective, Excellent for acute medication, Counteracts dry mouth. Health in Gum provides better chewing gum consistency to the medicated chewing gum. In the present study an attempt was made to formulate medicated chewing gum containing Ondansetron hydrochloride using as the health in gum base. Ondansetron prevents nausea and vomiting by reducing the activity of the center in the brain that controls nausea. It also prevents motion sickness by reducing excitability of neurons in the motion and balance center (vestibular region) of the brain.

Characterization of inclusion complex

A taste assessment study by sensory panel of human volunteers (n=10) was mentioned in table 3,

This indicated that when Ondansetron hydrochloride-sodium saccharin complex is formed in a molar ratio of 1:3, then the complex will give tasteless organoleptic character.

Table 3: Taste assessment of Ondansetron hydrochloride-Sodium saccharin.

Ondansetron hydrochloride: Sodium saccharin	Taste of complex
1:1	Slightly Bitter
1:2	Slightly bitter
1:3	Tasteless

Organoleptic and physical preformulation parameters

The UV absorption studies of Ondansetron hydrochloride were carried out in simulated salivary fluid of 6.6 pH. Ondansetron hydrochloride solution of 10 µg/ml concentration was scanned in the UV range from 200-400 nm range. It showed absorption maxima of 217 nm. Various parameters are mentioned in table 4.

Table 4: Preformulation parameters (organoleptic and physical).

Parameter	Observation
Color	White
Odor	Slight odor
Taste	Bitter
Appearance	Crystalline powder
Melting Point	177°C – 178°C
λ max(nm)	217 nm

In order to determine possible interaction between the drug, gum base and other ingredients used in the formulation, compatibility studies were conducted using FT-IR spectroscopy. There was no significant shift in the positions of the wave numbers when compared to that of the pure drug values. This indicated that there was no interaction between the drug and other excipient of the formulation.

Different formulations were prepared as per the procedure. Before punching of the powder mass into tablets different pre-compression characteristics of the powders was studied which includes bulk density, tapped density, Car's compressibility index, angle of repose, Hausner's ratio etc. The results of the tests are summarized in the table 5. The angle of repose for all the formulations was in the range of 26.10 to 27.50, Car's compressibility index of all the formulations was in the range of 11.20 to 12.66 and Hausner's ratio was in the range of 1.15 to 1.46.

Table 5: Pre-compression data of medicated chewing gum of Powder blends.

Batch No	Angle of repose (ɵ)	LBD (gm/ml)	TBD (gm/ml)	Carr's Index (%)	Hausner's ratio
A	27.39±0.03	0.59±0.06	0.71±0.01	11.20±0.07	1.18±0.01
B	26.11±0.01	0.61±0.06	0.73±0.01	12.66±0.05	1.15±0.02
C	27.36±0.07	0.66±0.04	0.76±0.01	12.58±0.09	1.46±0.06
D	27.10±0.05	0.45±0.04	0.75±0.02	12.47±0.04	1.21±0.05
E	28.11±0.04	0.76±0.03	0.77±0.01	11.46±0.05	1.23±0.02
F	27.50±0.01	0.75±0.01	0.76±0.02	11.45±0.06	1.19±0.02

Post-compression parameters

After compression, different post compression parameters like hardness, friability, weight variation and thickness of the formulations were determined. The results are summarized in table 6. The hardness was maintained between 3.83 to 3.36 kg/cm^2, resulting friability in the range of 0.24 to 0.47%. The weight variation was in the range of 500±0.73 to 500.95±0.45. The thickness of all the formulation was in the range of 5.31 to 5.54 and drug content is 99.24 to 99.96.

Table 6: Post-compression data medicated chewing gum.

Batch No.	Hardness** (kg/cm^2)	Friability# (%)	Weight variation. ***(mg)	Thickness* (mm)	Drug content* (%)
A	3.36± 0.12	0.43±0.01	501.5±0.56	5.36±0.02	99.67±0.01
B	3.63 ± 0.05	0.32±0.01	500.95±0.45	5.31±0.02	99.49±0.03
C	3.43 ± 0.10	0.24±0.01	501.3.±0.45	5.42±0.03	99.86±0.02
D	3.60 ± 0.12	0.24±0.01	500 ±0.73	5.54±0.02	99.28±0.02
E	3.86 ± 0.35	0.47±0.01	501±0.25	5.52±0.02	96.24±0.02
F	3.83 ± 0.02	0.33±0.01	500.75±0.84	5.51±0.02	99.96±0.02

In- *vitro* drug release study

The results obtained from the dissolution studies of various batches A, B, C, D, E, F. Among these batches, batch E and F showed cumulative drug release of 90.64% and 96.35% respectively within 12 min. A graphical presentations of dissolution study of all batches

were represented in table 7 and figure 2. Thus the dissolution study suggested that maximum amount of Ondansetron hydrochloride was released within 12 min in artificial saliva.

Table 7: *In vitro* dissolution study.

Time (min)	Batch A	Batch B	Batch C	Batch D	Batch E	Batch F
0	0	0	0	0	0	0
2	41.24±0.23	46.24±0.09	48.44±0.05	40.23±0.04	45.23±0.02	45.35±0.01
4	46.35±0.24	55.45±0.01	59.44±0.01	42.34±0.21	55.45±0.07	57.56±0.02
6	51.64±0.24	63.34±0.01	68.55±0.04	55.35±0.22	65.55±0.01	74.64±0.01
8	56.24±0.32	65.45±0.01	76.39±0.02	59.39±0.02	76.64±0.02	87.34±.0.01
10	63.22±0.34	72.55±0.02	81.39±0.01	67.97±0.02	82.64±0.07	92.64±0.02
12	66.27±0.06	73.35±0.02	86.47±0.01	71.54±0.01	90.64±0.05	96.35±0.05

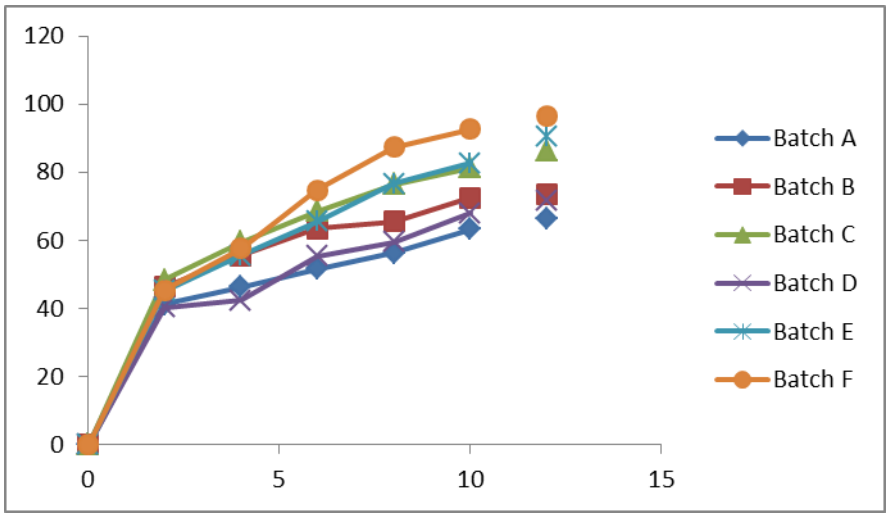


Fig. 2: *In-vitro* drug release.

Stability studies: As formulation E and F better drug release, only these 2 formulations are subjected to stability studies in which post compression parameters after stability are studied. Results of stability studies indicated that there is no change in post compression parameters and in vitro drug release study. Results are represented in table 8.

Table 8: Post compression parameters after Stability.

Batch	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Thickness (mm)	Drug content (%)
E	3.82	0.18	499.85	5.63	98.01
F	3.89	0.21	500.23	5.62	98.24

CONCLUSION

Medicated chewing gum of Ondansetron HCl was successfully prepared by direct compression technique. The formulation Batch F shows good properties to prepare a proper mixture for preparation of chewing gum. The weight variation, % friability of formulation batch F was found to be in acceptable limits and thus can be used for preparation of chewing gum. The eternal appearance of chewing gum shows that the batch F shows good gumminess, adhesiveness and springiness which are in the acceptable limits. The in-*vitro* study of chewing gum shows the release of 96.35% of drug within 12 min. Therefore medicated chewing gum of Ondansetron which is prepared will be a beneficial option for immediate and continuous release of drug and will change current scenario of dispensing Ondansetron HCl in future.

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