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Formulation Design and Evaluation of Chewing Gum of Anti-Emetic Drug

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HUMAN

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ABSTRACT

Aim of present work is development and evaluation of chewing gum of antiemetic drug (Domperidone). Domperidone is a dopamine antagonist with antiemetic properties. Domperidone has very low oral bioavailability (15%) owing to its extensive metabolism in liver and gut wall. In present study medicated chewing gum of domperidone was formulated to accelerate the onset of action and to improve the bioavailability so as to get quick relief from nausea and vomiting with greater patient compliance. In this study, ten formulations of domperidone were formulated as a chewing gum and best formulation was film coated. In each formulation, drug concentration remains the same and excipient concentration was varied. Direct compression method, wet granulation and direct compression with solid dispersion were used for the formulation. Different excipients such as health in gum, glyceryl monostearate, BHT, PEG-6000, titanium dioxide, talc, magnesium stearate, aerosil, sweeteners, flavours etc were used with other standard excipients. The prepared powder blend was evaluated for its preformulation characteristics viz, true density, bulk density, compressibility index, angle of repose, Hausner's ratio. The physical characters of tablet were evaluated viz; hardness, friability, weight variation, thickness, drug content, sickness, and in-vitro dissolution analysis. Optimized formulation F10 prepared by solid dispersion showed a drug release of 97.68% and assay 99.9%clearly complies with the standard values and F10 was film coated using HPMC.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site of the body, to achieve promptly and then maintain the desired therapeutic drug concentration. Medicated chewing gum is solid, single dose preparations that contain one or more ingredients that are released by chewing[1,2]. This drug delivery system provides benefits such as pleasant taste, fast onset of action and high bioavailability, higher patient compliance, ready for use and fewer side effects over tablets or liquid formulations**.**

Chewing gum is mixture of natural or synthetic gums and resins sweetened with sugar, corn syrup, artificial sweeteners and may also include coloring agents and flavors bulking agents, softening agents, antioxidants, glidants. Medicated chewing gums are prepared by different methods like direct compression method,[3] conventional/traditional method[4], cooling and grinding method.[5]

Antiemetic drugs are used to prevent or suppress vomiting[6]. They act by blocking several receptors located in vomiting centers such as H1 histaminic, dopamine D2, 5-HT3 receptor, muscarinic, and neurokinin1(NK1) receptors. Domperidone is a dopamine antagonist with antiemetic properties. Domperidone has very low oral bioavailability (15%) owing to its extensive metabolism in liver and gut wall. The biological half-life of domperidone is 7.5 hrs. and it may be given by mouth in doses of 10 to 20 mg three or four times daily up to a maximum daily dose of 80 mg. The aim of present research work was to formulate medicated chewing gum of domperidone to accelerate the onset of action and to improve the bioavailability so as to get quick relief from nausea and vomiting with greater patient compliance.

MATERIALS AND METHODS

MATERIALS

Domperidone maleate was received from Fourrts Pharma (Tamilnadu, India). Health in Gum was received as gift sample from CAFOSA (Barcelona, Spain). All other ingredients and solvents used were of analytical and pharmaceutical grade.

METHODS

Drug-excipient compatibility studies[7]

In the chewing gum dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug- excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may be present for known drugs. For new drugs or new excipients, the preformulation scientist must generate the needed information.

Physical observation:

Active ingredient was mixed well with all excipients in binary ratio and small portion of this mixed powder was placed in a cleaned and dried vial. This vial was kept for observation in stability chamber at 40°C± 2°C /75±5% RH. Physical observation has been carried out visually at the initial stage and after 30 days exposure to the stated condition. The results are tabulated in Table 4.

Table 1: Parameters for Physical Observations

S.NO	COMPOSITION	PARAMETER
1	Domperidone	Color change
2	Domperidone + Excipients	Color change

Chemical compatibility studies by FT-IR[8]

Physical compatibility studies were assured by FT-IR studies. The crude drug sample, drug-excipient mixtures of the formulation were chosen for the study. The FT-IR spectra of the above samples were studied after a period of 30 days from preparation of the mixtures, to facilitate prompt detection of incompatibility. The spectra were obtained by preparing Potassium bromide pellets under dry condition by using pellet press. The spectra of the crude drug sample and that of the drug-excipient mixtures were compared to check the incompatibility problems. If there are no changes in peaks of mixture when compared to pure drug, it indicates the absence of chemical interaction.

PREPARATION OF STANDARD CALIBRATION CURVE OF DOMPERIDONE[10]

Preparation of standard stock solution of Domperidone (100µg/ml)

About 63.5 mg of domperidone maleate equivalent to 50mg of domperidone was weighed accurately and transferred to 50 ml volumetric flask and dissolved in about 20 ml of 0.1N HCl. The volume was then made up to the mark with 0.1N HCl. 1 ml of this solution was transferred to 10 ml volumetric flask and diluted up to 10 ml with 0.1N HCl. This solution contained 100 µg of drug per ml of solvent.

Preparation of calibration curve for Domperidone at 284 nm.

0.5, 1.0, 1.5, and 2.0 ml of the standard stock solution were pipetted out into a series of 10 ml volumetric flask. The volumes were made up to the mark with 0.1N HCl and mixed to obtain solutions in the concentration range of 5, 10, 15, and20 µg/ml of drug. The absorbance of these resultant solutions was measured at 284 nm against 0.1N HCl as blank and a graph was plotted between absorbance obtained and the concentrations of the solutions. The Lambert-Beer's law was obeyed in the concentration range of 5 to 20 µg/ml at 284 nm as shown in Figure 3.

TRIAL NOs 1 & 2 BY USING WET GRANULATION METHOD

Accurately weighed quantity of domperidone maleate equivalent to domperidone, Health in gum®, butylated hydroxytoluene, microcrystalline cellulose, lactose glyceryl monostearate, talc, magnesium stearate titanium dioxide, acesulfame potassium, aspartame, aerosil, flavor and colour were passed through the mesh. The sifted domperidone maleate is granulated with Micro crystalline cellulose and Lactose. The binder solution was prepared by dissolving povidone, Butylated Hydroxytoluene and erythrosine supra in water. The binder solution was poured to the dry mix and mixed well to get a uniform mass. The granules were dried in an oven. The dried granules were passed through sieve and collected in poly bag. The sifted flavour was added to the above dried granules and mixed for 5 minutes. The sifted gum base was added to the flavoured granules and mixed for 10 minutes. To above mixture Glyceryl Monostearate, Titanium dioxide, Talc, Acesulfame potassium, Aspartame, Aerosil, were added and mixed. Finally, the sifted Magnesium stearate was added to the above granules and mixed for 3 minutes. The final blends of granules were compressed into domperidone Medicated Chewing Gum using 13.5mm round shaped punch.

TRIAL NOs 3 TO 8 BY USING DIRECT COMPRESSION METHOD

Accurately weighed quantity of domperidone maleate equivalent to domperidone, Health in gum, talc, magnesium stearate, butylated hydroxytoluene, glyceryl monostearate, titanium dioxide, acesulfame potassium, aspartame, aerosil, flavor and colour were passed through the sieve. The sifted domperidone maleate is added to the sifted flavor and mixed for 5 minutes. The sifted gum base was added to the flavoured dry mix and mixed for 10 minutes. The Glyceryl Monostearate, Titanium dioxide, Talc, Acesulfame potassium, Aspartame, Butylated Hydroxyltoluene, Erythrosine supra, Aerosil, are separately mixed and this mixture is added to the above blended mix and mixed for 10 minutes. Finally, the sifted Magnesium stearate was added to the above mixture and mixed for 3 minutes. The final blend of powder was compressed into Domperidone Medicated Chewing Gum using 13.5mm round shaped punch.

TRIAL NOs 9 & 10 BY USING SOLID DISPERSION TECHNIQUE

To increase the solubility of domperidone, the solid dispersion of domperidone is made using Poly ethylene glycol 6000 in different ratios (1:0.5, 1:1) by fusion method. The completely fused blend was passed through 100# to get uniform sized particles of domperidone solid dispersion. Accurately weighed quantity of, Health in gum®, butylated hydroxyltolune, glyceryl monostearate, magnesium stearate, titanium dioxide, talc, acesulfame potassium, aspartame, flavour, colour and aerosol were passed the through mesh. The sifted domperidone maleate solid dispersion is mixed with the sifted flavour. The sifted gum base was added to the flavoured solid dispersion mix and mixed for 10 minutes. The Glyceryl Monostearate, Titanium dioxide, Talc, Acesulfame potassium, Aspartame, Butylated Hydroxyltolune, Aerosil, Erythrosine supra are separately mixed and this mixture is added to the above gum base solid dispersion mix and mixed for 10 minutes. Finally, the sifted Magnesium stearate was added to the above mixture and mixed for 3 minutes. The final blend of powder was compressed into domperidone Medicated Chewing Gum using 13.5mm round shaped punch.

Table 2: Composition of different batches of domperidone chewing gum

Ingredients	F1 (mg/MCG)	F2 (mg/MCG)	F3 (mg/MCG)	F4 (mg/MCG)	F5 (mg/MCG)	F6 (mg/MCG)	F7 (mg/MCG)	F8 (mg/MCG)	F9 (mg/MCG)	F10 (mg/MCG)
Domperidone	12.72	12.72	12.72	12.72	12.72	12.72	12.72	12.72	12.72	12.72
Health in gum®	756.88	735.38	825	817.38	816.88	816.38	815.88	815.38	804.02	787.66
Glyceryl Mono stearate	70	80	90	85	80	75	70	65	70	80
Aspartame	30	30	30	30	30	30	30	30	30	30
Acesulfame potassium	25	25	25	25	25	25	25	25	25	25
BHT	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Tartrazine yellow			0.75	0.75						
Erythrosine supra	0.75	0.75	-	-	0.75	0.75	0.75	0.75	0.75	0.75
Orange Flavour	-		2.88	-	-		-	-	-	-
Flavour-Mixed fruit	10	10		10	10	10	10	10	10	10
TitaniumDioxide	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Talc	60	70	50	55	60	65	70	75	75	75
Magnesium stearate	5	6	5	5	5	5.5	5.5	6	6	6
Aerosil	2	2.5	1	1.5	2	2	2.5	2.5	2.5	2.5
PEG-6000	-	-	-	-	-	-	-	-	6.36	12.72
MCC	35	35	-	-	-	-	-	-	-	-
Lactose	30	30								
Povidone k-30	5	5	-	-	-	-	-	-	-	-
Water (12%)	3ml	3ml	-	-	-	-		-	-	-
Total Weight(mg)	1050	1050	1050	1050	1050	1050	1050	1050	1050	1050

*12.7 mg of Domperidone maleate=10 mg of Domperidone

Composition of Ingredient for film Coating:

2% coating has been given for the best formulation. The coating materials are planned to coat the chewing gum for protecting the chewing gum from moisture, for providing a uniform colour and also for getting a mild sugar coat.

Table 3: Composition of film coating material

Sr. No.	Ingredients	Quantity/1kgchewing gum (gm)
1	HPMC-15 cps	18.86
2	Titanium Dioxide	9.80
3	Propylene glycol	1.89
4	Talc	3.77
5	Erythrosine lake	7.28
6	Sucrose	13.44
7	Purified water	323.75

Preparation of film Coating solution:

Hypromellose 15 cps was dispersed in 250 ml of hot water. Titanium dioxide, Talc, Erythrosine lake were passed through #60 and triturated separately in a mortar and added 50 ml purified water to the mixture and mixed well and added to the Hypromellose solution under stirring and mix it. Sucrose was dissolved in 23.75ml of purified water and added to the above mixture and mixed well for 15 minutes and finally, propylene glycol was added and mixed well. Finally, the solution was filtered through #200 nylon cloth, mixed well and transferred to pressure vessel. The core chewing gums are de-dusted and transferred to the coating pan and are coated using the solution.

Evaluation Studies:

Pre-compression study: The blend which is made into chewing gum by direct compression method was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.

Post compression study[11, 12].

Weight variation: According to specifications, from weight of 20 chewing gums average weight and standard deviation is calculated.

Hardness: Due to absence of any reported method, it was decided to use the Monsanto type hardness tester for determination of hardness of all MCG formulations. The average values, standard deviation and relative standard deviation were calculated.

Thickness: Chewing gum thickness is an important parameter to be controlled to facilitate packaging. Chewing gum thickness must be controlled within a ±5% variation of a standard value. Any variation within a particular lot should not be apparent to the unaided eye of the consumer. Thickness of all the formulations was measured using a digital vernier.

Friability[13,14] Friability is a measure of the resistance of the chewing gum to abrasion. Friability test carried out with Roche friabilator. Twenty chewing gums were weighed accurately and placed in the friabilator and was operated for 100 revolutions for 4 minutes. The chewing gum is then de-dusted and weighed. The weight loss of 0.5 to 1% is considered as acceptable limits for conventional chewing gum.

Stickines:[15] The MCG was placed on the plain surface, Teflon hammer (250 gm) collide on it for period of ten minutes at a frequency of about 30 / minute. Any stick of mass to hammer surface was observed and reported after 10 minutes.

Assay: For estimation in dosage form, 20 chewing gums were weighed and powdered. Amount equivalent to 25.4 mg of domperidone maleate from powdered formulation was accurately weighed and taken in 100ml volumetric flask, diluents were added and sonicated for 20 minutes. After sonication, the solution was stirred with magnetic stirrer for 10minutes and cooled the solution to room temperature and make up the volume with diluents and filtered. From this 5ml of stock solution were diluted into 100ml with 0.1NHCl. Absorbance of solution was measured at 284nm.

***In-vitro* drug release studies**[16,17]**:** In order to study the *in-vitro* drug release pattern from chewing gums, it was necessary to design an apparatus, which could give same impact on gums. This was necessary in order to simulate the human mastication. After an extensive literature survey and discussion, it was decided to modify the I. P. disintegration test

apparatus. The modified apparatus which mimics the human chewing behavior was used to determine the drug release. *In-vitro* drug release for the prepared formulations was carried out using Modified disintegration apparatus. These studies are carried out in 0.1N HCl.

Procedure: 1 g of formulation was adhered on to the wooden block which was placed in the glass beaker containing 200 ml of 0.1N HCl. Samples were withdrawn at 5, 10,15,20,30 min. of intervals. Collected samples were estimated by UV visible Spectrophotometer at 284 nm.

RESULTS AND DISCUSSION

DRUG-EXCIPIENTS COMPATIBILITY

It was determined as per procedure and results are summarized in Table 4.

Table 4: Physical observation in compatibility study

Sr. No.	Composition	Initial	1st week	2nd week	3rd week	Inference
1	Domperidone	White	NCC	NCC	NCC	Complies
2	Domperidone + Excipients	Light pink	NCC	NCC	NCC	Complies

NCC- No Characteristic Change.

Discussion

From the drug excipients compatibility study, it was observed that there was no change or interaction between drug and excipients. Thus it was concluded that the excipients selected for the formulation were compatible with domperidone.

IR spectral analysis:

FT IR analysis was carried out for pure drug and drug excipient mixtures

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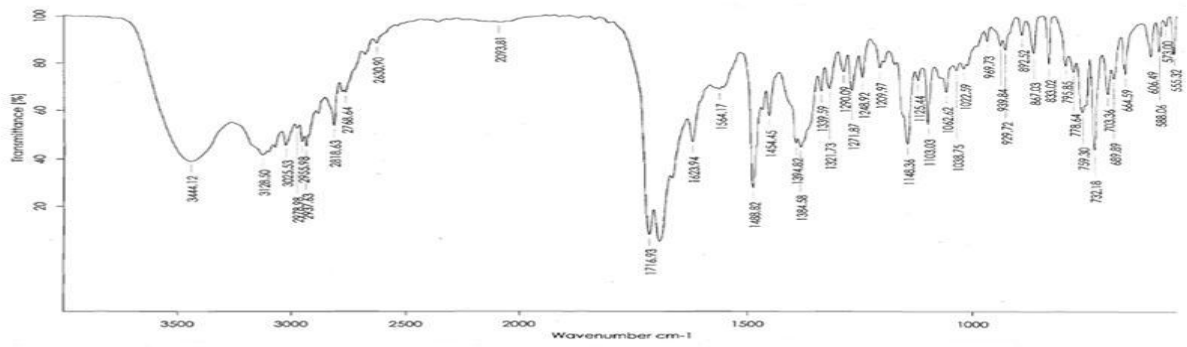

Figure -1 FTIR Spectrum of Domperidone maleate

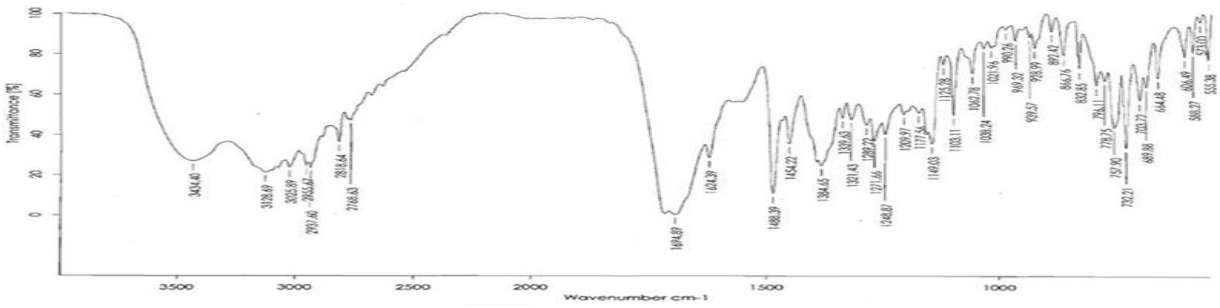

Figure -2 FTIR Spectrum of Domperidone maleate with excipients

FT IR spectrum of drug shows the prominent peaks with respect to the functional groups. The FTIR spectrum of drug and physical mixture of drug with excipient concluded that there is no significant interaction between the drug and excipients. In the spectrum of drug-polymer mixture, the characteristic peak of drug was not altered.

Calibration curve of pure Domperidone

Calibration curve of pure domperidone in 0.1 N HCl was determined as per the method**.** The calibration curve showed a regression value (R^2) of 0.9959.

Table 5: Reading of absorbance of standard solution

Sr. No.	Concentration (µg/ml)	Absorbance(at 284 nm)
1.	5	0.3121
2.	10	0.5367
3.	15	0.7241
4.	20	0.9876

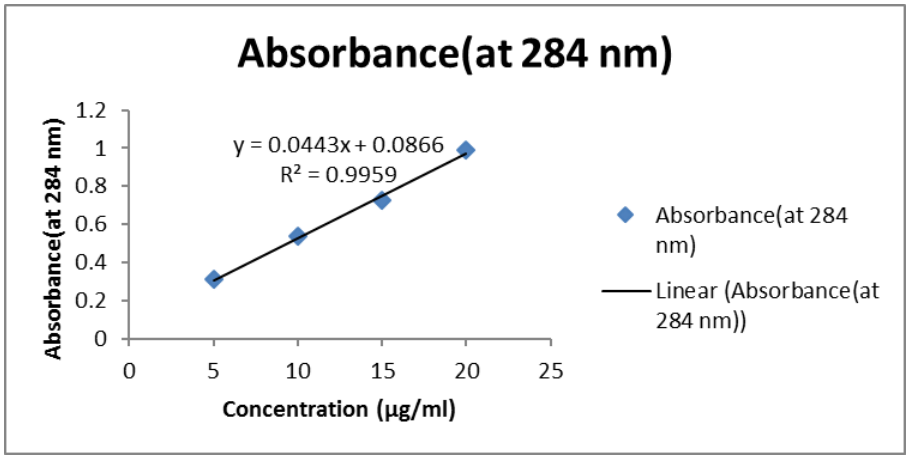

Figure 3: Calibration curve of domperidone in 0.1N HCl

Pre-compression Evaluation of the Powder Blend:

Bulk density for powder blend was found to be in between 0.391 to 0.454. The values were found in the direct compression method. Tapped density was found to be in between 0.506 to 0.586. Compressibility index for powder blend was found to be in the range of 13.65 to 23.74. Hausner's ratio for powder blend was found to be in between 1.15 to 1.42. From the observed values, the flow type was found to be good for direct compression method. Angle of repose for powder blend was found to be between 28º.16'to 34º.40´, which is well within the specification limit of 30º to 35º and the flow type was found to be good.

Formulation Development

After the preformulation studies, the prepared powder blend was compressed into chewing gum by direct compression method.

Figure 4: Uncoated chewing gum

Post-Compression Parameters of Medicated chewing gum

Table 6: Post-Compression Parameters of Medicated chewing gum

Formulation Code	Average weight	Thickness (mm)	Hardness (kg/cm2)	Friability(%)	Weight variation	Assay(%)	Stickiness
F1	1050	6.68±0.16	4	0.36	1050±5	99.34	Non
F2	1050	6.85+0.01	4	0.40	1050±5	99.2	Non
F3	1050	6.38±	4	0.39	1050±5	99.01	Non
F4	1050	6.58±	4.5	0.31	1050±3	99.85	Non
F5	1050	6.81±0.16	4.5	0.35	1050±3	99.5	Non
F6	1050	6.66 ±	4	0.33	1050±5	99.9	Non
F7	1050	6.45±	4	0.32	1050±6	99.2	Non
F8	1050	6.58±	4.5	0.35	1050±4	98.98	Non
F9	1050	6.75±	4	0.38	1050±2	99.28	Non
F10	1050	6.71±	4	0.29	1050±3	100.21	Non

The thickness of the chewing gums was found to be in the range of 6.4 to 6.8 mm. The prepared chewing gums in all the trials possessed good mechanical strength with sufficient hardness in the range of 4.00 to 4.50kg/cm^2. The friability of the chewing gum was found to be within 1%. None of the formulations were found to be sticky. The average weight of the formulations was found to be 1050mg. It is within the permissible range (± 5%deviation). The percentage of drug content was found among different batches of the chewing gums and ranged from 98.5 to 101.0 which was within the acceptable limit. All evaluated parameters values are found to be within limits.

***In-vitro* drug release**

Table 7: Cumulative% drug release in different trials

Formulation Code	Cumulative% drug release in different trials				
	Simulated gastric fluid (0.1 HCL)				
	05	10	15	20	30
F1	70+ 0.31	75+0.32	80+0.27	84.2+0.78	90.17+0.32
F2	68±0.25	73.21+0.45	79.51+0.13	84.09+0.57	89.21+0.43
F3	65.46±0.	74.1+0.32	81.09+0.78	83.97+0.52	90.1+0.95
F4	68.29±0.	74.84+0.18	78.74+0.52	81.82+1.35	86.24+0.72
F5	71.83±0.	75.09+0.52	81.76+0.26	83.76+0.34	87.21+0.66
F6	73.00±0.	76.58+0.13	80.72+0.43	85.80+0.78	88.51+0.57
F7	71.00±0.	74.38+0.13	79.72+0.36	84.80+0.62	89.51+0.42
F8	72±0.46	76.58+0.18	81.72+0.53	87.80+0.362	91.51+0.26
F9	72±0.32	82.61+0.15	88.64+0.62	92.36+0.488	95.32+0.56
F10	71.86±0.	75.14+0.21	91.24+0.56	95.12+0.728	98.70+0.21

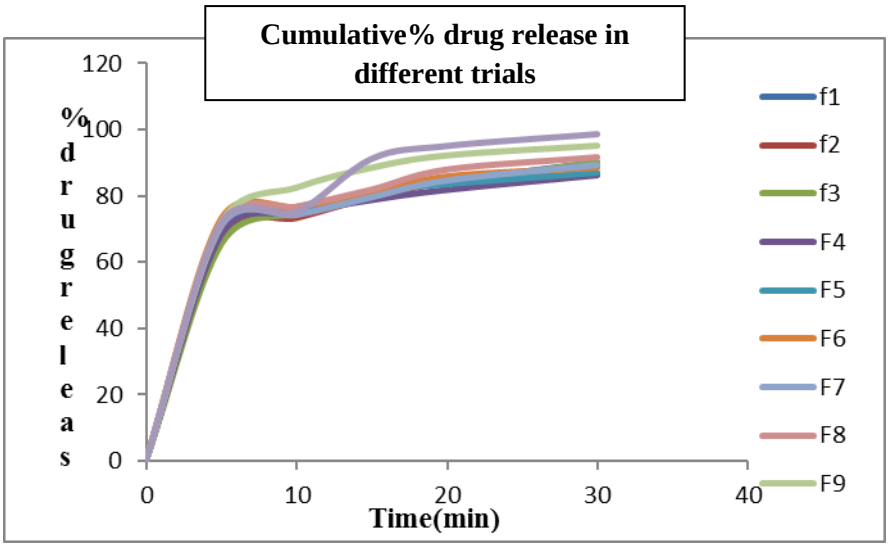

Figure 5: Cumulative% drug release in different trials

Domperidone maleate medicated chewing gum of the trial (F10) satisfied all the parameters and showed a good *in-vitro* drug release rate 99.88±0.21%. It was coated by film coating

method. The coated chewing gum was evaluated for the following parameters including thickness, weight variation, and assay and *in-vitro dissolution* studies.

The evaluation of coated chewing gum:

Figure 6: Coated chewing gum

The evaluation of prepared domperidone coated chewing gums was carried out as per the methods described. The results are shown in Table 8.

Table 8: Evaluation of coated tablet

Trial	Thickness (mm)	Weight variation (mg)	Hardness (kg/cm^2)	Assay (%)	Stickiness	*In-vitro* Drug release (%)
F10	6.74 ± 0.14	1072±2	4	99.9±0.80	Non sticky	97.68±0.80

Discussion:

The thickness of the coated chewing gums was in the range of 7.08±0.02 mm. This is due to the film coating. The prepared coated chewing gums in all the trials possessed good mechanical strength with sufficient hardness in the range of 4.00kg/cm^2.The average weight of the coated formulations was found to be 1072±2mg. It is within the permissible range (± 5%deviation). The percentage of drug content was found to be 99.9% which was within the acceptable limits. Coated domperidone medicated chewing gum of the trial (F10) showed a good *in-vitro* drug release rate of 97.68±0.80%.

COMPARATIVE DATA OF UNCOATED AND COATED MEDICATED CHEWING GUM

Table 9: Comparison of uncoated and coated medicated chewing gum

Trial	Thickness (mm)	Weight variation (mg)	Assay (%)	*In-vitro* Drug release (%)
F10-Un coated	6.71 ± 0.14	1050±3	100.21	98.70±0.21
F10-Coated	6.74±0.11	1071±2	99.9±0.80	97.68±0.80

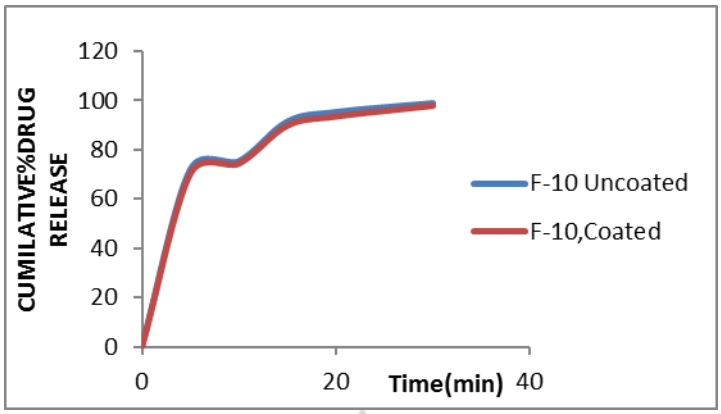

Figure 7: Comparative dissolution of uncoated and coated medicated chewing gum

Domperidone coated chewing gums were compared with the same trial of uncoated domperidone MCG. The thickness of film coated chewing gum was found to be more than uncoated MCG. Weight variation was increased in film coated MCG than the uncoated chewing gums. This was due to the coating of core MCG. The assay and *in-vitro* drug release of coated chewing gum were found to be within the limits.

Optimized formulations were kept for stability studies as per ICH guidelines at 25±2°C/60±5% RH, 40±2°C/75±5% RH. Then the stability results of best formulation after 180 days were compared with their initial results, it was found that there was no significant difference in drug content of optimized formulations.

CONCLUSION

In the present study, an attempt was made to prepare medicated chewing gum of domperidone. The gum was prepared Health in gum®Gum Base and with other standard excipients. The chewing gum was prepared by direct compression, direct compression with

wet granulation and direct compression by solid dispersion. Pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio of powder blend and pure drug were evaluated and results were compared. The results showed that the blend of mixture had good flow property and packing ability. FTIR studies showed that there was no marked incompatibility between Domperidone and excipients. The percentage drug release of F1 to F10 was 89.21 to 99.88% at the end of 30 minutes. F10 formulation showed release of 99.88% at the end of 30 minutes. The results concluded that the chewing gum that contains solid dispersion of domperidone and PEG showed good release. It indicates that PEG acts as a good solubilizer which solubilizes the drug Domperidone. Higher polymer ratios enhance drug solubility, which leads to increase in the amount of drug absorption. By delivering Domperidone in the form of chewing gum, it directly enters into systemic circulation thus bypasses First Pass Metabolism and hence Bioavailability of drug increases and the optimized formulation F10 was selected for film coating and finally the coated chewing gum were analyzed for assay and dissolution. The drug release from the coated chewing gum was found to be 99.68±0.80%. The present study concluded that Domperidone chewing gum formulation is very acceptable for patients.

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