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Formulation and Evaluation of Medicated Chewing Gum of Itopride HCl as an Anti-Emetic Agent

Dr. G. Govind Reddy*, J Sushma, Chinmayi, Ganesh K, Kalyani V, Keerthi L Deshpande

Department of Pharmaceutics, Togari Veeramallappa Memorial College Of Pharmacy, Kolagal Road, Bellary 583101, Bellary, Karnataka, India.

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ABSTRACT

Aim: The aim of this study was the formulate and evaluate of medicated Chewing gum of ITOPRIDE HCl an Anti-emetic agent by Direct Compression mould method. Medicated chewing gums are intended to be chewed and act either locally or absorbed via buccal mucosa. The ITOPRIDE HCl chewing gum was prepared to overcome diarrhoea, abdomen discomfort and motion sickness. **Materials and Methods:** ITOPRIDE HCl medicated chewing gum was prepared by softening gum bases and then mixing with other ingredients like Glycerol, Poly vinyl pyrolidine (PVP), Sucrose etc in different concentrations. All studies were performed like hardness, stickiness, weight variation, friability, in vitro drug release test and FTIR to determine the physiochemical characteristics. **Result:** The proportion of gum base was increased the hardness of chewing gum was observed. The formulation F5 showed maximum in vitro drug release. i.e., 97.15% compared to other formulations. **Conclusion:** Evaluation was carried out to all the formulations in batches along with the stability studies showed satisfactory results. The formulation of ITOPRIDE HCl into medicated chewing gum was done successfully.

KEYWORDS: Itopride HCl, FTIR, friability, buccal mucosa, physiochemical.

INTRODUCTION

Medicated chewing gums are solid, single dose preparations that contain one or additional active ingredients that are released by chewing[1]. Aspirin chewing gum was the first medicated chewing gum produced in the US. Since then, the medicated chewing gums have been available in the market. Nicotine gum was introduced during the 1970's in which the potential of chewing gum as a drug delivery system was recognised. In 1991, chewing gum was approved as a term for pharmaceutical dosage form by the Commission of European council[2].

Chewable tablets and chewing gums have been readily acceptable by the parents for use in children with full dentition. Particularly children may consider chewing gum as a more preferred method method of drug administration compared to oral liquids and tablets; Hence attempt is made to prepare medicated chewing gum to increase its compliance[3].

Medicated chewing gum is a novel drug delivery system containing masticatory gum base with pharmacologically active ingredient and is intended to use for local treatment of mouth diseases or systemic absorption through oral mucosa. It is oral drug delivery system which is very simple, most convenient, safest, non invasive, and most economical, it continues to be the the preferential route of administration. The intraoral route is the most preferred due to its convenience and rapid onset of action[1].

Medicated chewing gums are appropriate for the treatment of diseases of the oral cavity and the throat because they can retained within the mouth for an extended period of time[4]. Using chewing gum their increase in saliva and amplifies buffer system in the mouth that helps neutralise the acidic situation and increase rebuilding the external coverage of teeth[7]. Chewing gum also has proven value as a delivery vehicle for pharmaceutical and nutraceutical ingredient. Today chewing gum is convenient drug delivery system which is appropriate for a wide range of active substances[5].

The chewing gum is on of the new methods of oral transmucosal drug delivery and is a useful tool for systemic drug delivery. Advantages of chewing gum over conventional drug delivery system includes:

- Rapid onset of action

- High bioavailability
- Easy consumption without the need of water
- Higher patient compliance
- Fewer side effects like dry mouth and decrease in toxicity[6]

There are many factors which should be considered for this formulation like contact time of formulation with the oral mucosa. Physicochemical properties of drug which plays a major role in drug release from the chewing gum formulation. Formulation factors like composition, amount of gum base and even type of the gum base affect rate of release of active ingredient[7]. Problem with chewing gums is that they have synthetic gum bases which are not biodegradable in nature. Although natural gum bases such as gliadin, a protein of wheat grain also known as prolamin can be used in gum due to its good chew ability[5].

The most common method to administer drug is oral route, in which the drug is swallowed and it enters the systemic circulation. There are various dosage forms those can be administered orally. Out of which, chewing gum is most popular. It is potential useful means of administering drugs locally and systemically[8].

Itopride Hydrochloride is an oral prokinetic agent used in the treatment of gastric motility disorder. It is the benzamide derivative, absorbed from gastrointestinal tract. Itopride Hydrochloride activates the gastrointestinal motility through synergism of its Dopamine D_2 receptor antagonistic action and its acetylcholinesterase-inhibitory action. In addition to these actions, Itopride has an antiemetic action, which is based on its dopamine D_2-receptor antagonistic action. The short biological half-life (6 hr), 60% bioavailability and dosage frequency more than once a day (50 mg) make the Itopride Hydrochloride an ideal candidate for the novel drug delivery systems[9]. Itopride Hydrochloride, an antiemetic agent can be incorporated into medicated chewing gum to provide relief from nausea, vomiting and motion sickness. To increase patient compliance, a Medicated chewing gum formulation is desirable.

General Composition of the Medicated Chewing Gum[1]

Table 1: Composition of Medicated Chewing gum

Active Agent	**Approximately 50%**
Chewing Gum base	15-45%
Plasticizers	0.5-15%
Sweeteners	Up to 60%
Flavouring agents	0.01-1%
Lubricants	0.2-1%
Colouring agent	<0.1%
Adjuvants	Up to 50%

- **Active agent:** In medicated chewing gum active pharmacological agent may present in core or coat or in both. A saliva soluble present ingredient will be completely released within 10-15min of chewing whereas lipid soluble ingredient will dissolve in the gum base and thereafter be slowly and completely absorbed.

- **Chewing gum base:** It is the base of medicated chewing gum, mainly classified as natural or synthetic gum base. Ex: Bees wax, prolamin, Health in gum, etc.

- **Plasticizer:** These are to regulate cohesiveness of product. They are divided into natural plasticizers and synthetic plasticizers. Ex: Glycerin, Aspartame, etc.

- **Sweeteners:** They are used for soothing taste on tongue, softeners to blend the ingredients and retain moisture. They are divided into aqueous sweeteners and bulk sweeteners. Ex: Sucrose, Dextrose, etc.

- **Colouring agents:** It includes FD and C type dyes and lakes, fruit and vegetable extracts. Ex: Natural colours, Synthetic colours, etc

- **Flavouring agents:** They are used to improve flavour in the medicated chewing gum. It includes mint oil, peppermint oil, etc.

- **Lubricants:** Helps the blend from sticking. Ex: Magnesium sterate, etc.

MATERIALS AND METHODS

Materials

Itopride Hydrochloride was bought from yarrow chemicals LBS Mary Ghalkopar (west) Mumbai and all other chemicals and solvents were of analytical grade.

Methodology[10]

Common methods used for production of medicated chewing gum are**:**

- Direct Compression Method
- Melting Method/ Conventional Production Process
- Cooling, Grinding and Tableting Method
- Spray Drying Method
- Freeze Drying Method
- Trituration Method
- Fusion Method

Method of preparation

Medicated chewing gums were prepared by direct compression mould method. In this method each ingredients were weighed accurately and separately. Itopride Hydrochloride Bees wax, glycerol, Sucrose, Calcium Carbonate, Peppermint Oil, and PVP, all these ingredients were mixed thoroughly in Ascending order of their weights in a mortar. After proper mixing, ingredients smoothly grounded in a mortar and pestle and then previously weighed quantity of Bees wax was melted and added. Then whole mixture was again mixed thoroughly in pestle and mortar. After mixing and grinding the mixture was subjected for compression into desired moulds and pressed to form Medicated Chewing gum. After removing from mould, formulated Chewing gums were weighed and wrapped properly. Optimization of various selected batches of Medicated chewing gum by changing concentrations of different excipients as depicted in table 2.

UV –Spectroscopy of Itopride hydrochloride[4]:

Construction of standard calibration curve using a phosphate buffer 7.4 pH as a solvent:

50mg of pure drug Itopride hydrochloride was accurately weighed and transferred into 50ml volumetric flask. The volume was made up by using phosphate buffer 7.4pH at room temperature(stock solution 1) from this 10mlwas diluted to 50ml using phosphate buffer 7.4 pH (stock solution 2). 1ml, 2ml, 3ml, 4ml and 5ml of stock solution 2 was further diluted to 10ml with phosphate buffer 7.4pH to get stock solution of 0.5 µg/ml, 1µg/ml,1.5µg/ml,2µg/ml and 2.5µg/ml.

Preparation of stock solution:

From the stock solution of 1and 2, serial dilution was made to get 1, 2, 3, 4, 5 µg/ml solution using phosphate buffer 7.4pH as dilution medium. The absorbance of these solutions was measured against phosphate buffer 7.4pH as blank in UV vis spectrophotometer at 258nm. A standard graph was drawn using these values.

Drug excipients compatibility studies[12]:

FTIR can be used to investigate and predict any physiochemical interaction between different excipients. IR spectra matching approach was used for detection of any possible chemical interaction between the drug and excipients. A physical mixture of drug

and excipients were prepared. It was scanned from 4000 to 400cm^{-1} in a FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and physical mixture and peak matching was done to detect any appearance or disappearance of peaks.

PREFORMULTION EVALUATION[11]:

The measurement of Hauser`s ratio, Bulk density, Tapped density, Compressibility index, and Angle of repose was used to assess the flow characteristics of the gum base and drug excipient mixes.

- **Angle of repose:**

Using the tilting box, fixed tunnel, rotating cylinder, or hollow cylinder methods- all of which containers with a sample and raise them gradually so that the sample builds up and forms a conical heap on the surface one can ascertain the angle of repose. The angle of repose is used to measure the flow properties. It is described as the greatest angle that can exist between a powder pile`s surface and horizontal plane. The angle of repose and the powder flow are as follows:

$$tan\theta = \frac{h}{r}$$

Where, h= Height of the pile

r= Radius of the base of the pile

θ= Angle of repose

- **Bulk density:**

A powder`s bulk density can be found by measuring the mass of a known volume of powder that has been passed through a volumeter into a cup or by measuring the volume of a known mass of powder sample that has either been passed through a sieve into a graduated cylinder.

The mass of an aggregate per unit volume is known as bulk density, or unit weigh. It is stated in kg/liter.

The formula is used to determine the material`s bulk density is:

$$pb = \frac{M}{V}$$

where, pb = Bulk density

M = Weight of the container

V = Container volume

- **Tapped density:**

The measuring cylinder or vessel is mechanically tapped after the initial powder volume or mass is measured, and volume or mass readings are taken until a little more change in volume or mass is seen. The higher bulk density that results from mechanically tapping a container holding the powder sample is known as the “tapped density”. The formula used to determine the material`s tapped density is:

$$pt = \frac{M}{Vt}$$

where, pt = Tapped density

M = Weight of the powder

V = Minimum volume occupied after tapping

- **Compressibility Index and Hausner Ratio:**

The bulk density and tapped volume of the powder are measured in order to calculate the compressibility index and Hausner ratio. The basic process is to measure the unsettled apparent volume, or the final tapped volume, of the powder after tapping the material until no further volume changes occur, although there are various differences in the method of computing the compressibility index and Hausner ratio. Here is how to compute the compressibility index and Hausner ratio:

$$compressibility\ index = 100 * \frac{pt - pb}{pb}$$

Where, pt = Tapped density

pb = Bulk density

$$Haunser\ ratio = \frac{pt}{pb}$$

Where, pt = Tapped density

pb = Bulk density

POST FORMULATION EVALUATION[13]:

- **Organoleptic properties:** such as colour, odour, surface texture and appearance were observed[23].

- **Stickiness:** The formulated medicated chewing gum base was placed on plain surface. A mass of 250gm was hammered on it up to 10min. The frequency of hammering was about 30min[23].

- **Hardness:** It was determined by Monsanto hardness tester and the average hardness and standard deviation were caluculated[18].

- **Weight uniformity test:** Ten chewing gums were randomly selected among chewing gums, and the mean weight of 10 samples was determined. The chewing gums weighed should not differ with the mean weight over 5%[6].

- **Friability:** Medicated chewing gum tend to cup during handling and transportation which affects the quality, appearance, drug content, coating requirements and hence friability test is carried out. The apparatus used is Roche friabilator, which consists of a rotating disk of 12 inch diameter rotating at speed of 100rpm. 10 gum units to be evaluated are added into disc and rotated for 100 revolutions at 25rpm. The difference in weight represents the friability percentage (F%) that can be calculated based on formula:

$$F\% = (W_{initial} - W_{final} / W_{initial}) * 100$$

Note: MCGs pass the friability test if the F% is less than 1%[23].

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➢ **Drug content[14]:** Randomly 10 medicated chewing gums were taken, in a mortor and add 20 ml of 7.4 phosphate buffer crushed , sonicated, filter the solution and record the absorbance using UV spectrophotometer at 258nm.

➢ **In vitro drug release studies[15]:** After extensive literature survey, disintegration apparatus was slightly modified for this study. The modified apparatus which mimics the human chewing behaviour was used to determine the drug release. The MCG placed in 500ml of 7.4pH phosphate buffer and samples were collected periodically for each interval of 5, 10, 15, 20, 25 and 30min and absorbance was measured at 258nm. Measurements were carried out in replicated and mean standard deviation values are recorded[12].

Table 2: Formulation of Itopride Medicated gums by direct compression method

Formu-lation	Gum base (mg)	PVP (mg)	Glycerol (mg)	Sucrose (mg)	Peppermint oil (mg)	Drug-Active Ingredient (mg)	Calcium Carbonate (mg)
F1	240	400	32	240	12	10	88
F2	280	400	48	240	12	10	72
F3	300	400	64	240	12	10	56
F4	320	400	32	240	12	10	88
F5	350	400	48	240	12	10	72
F6	370	400	64	240	12	10	56
F7	400	400	32	240	12	10	88
F8	430	400	48	240	12	10	72
F9	450	400	64	240	12	10	56
F10	500	400	32	240	12	10	88

RESULTS AND DISCUSSIONS

Drug-excipient compatibility studies

FT-IR studies:

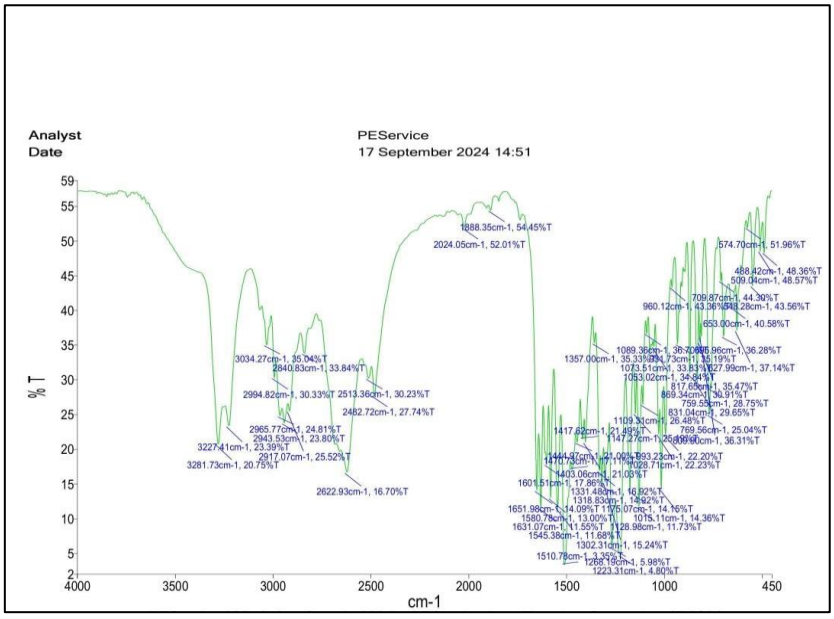

Figure 1: Fourier transform infrared spectra of pure drug

The FT-IR spectrum of pure drug and optimized formulations was shown in figures 1 and 2. FT-IR spectra results showed that same peaks were observed for pure drug and optimised formulation, and there are no additional peaks are observed. Therefore, from FT-IR spectra, it could be concluded that there is no compatibility between drug and excipients.

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Table 3: FTIR spectrum of ITOPRIDE HCl

Sl.no	Standard Value(cm^{-1})	Observed Value(cm^{-1})	Interpretations
1	3227.41-3034.27	3281.73	C-H Bending
2	1888-2482.72	2024.53	C-N Bending
3	1.268-1257	1331.48	C-O Bending
4	488.42-548.28	509.04	Alkyl halides stretching

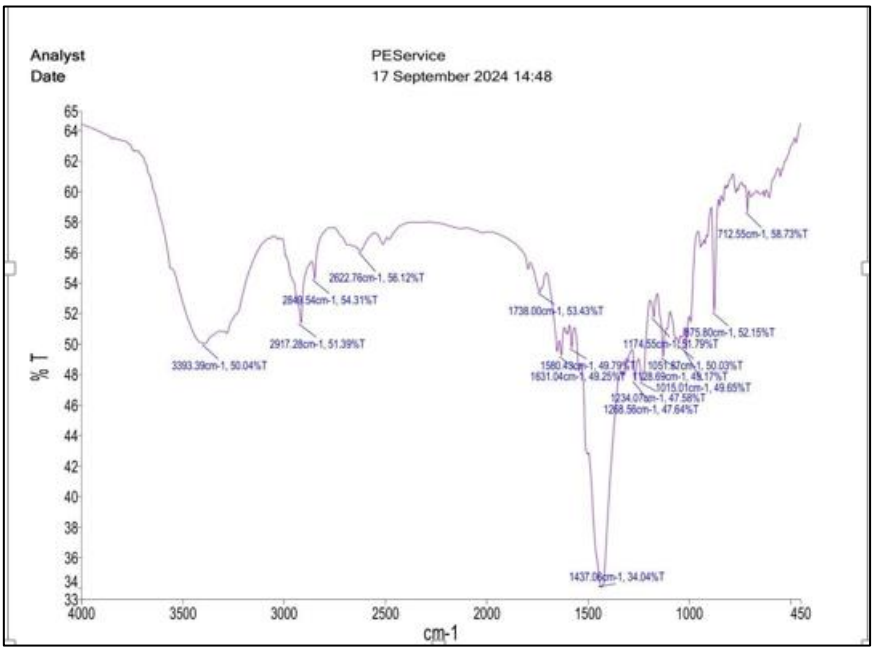

Figure 2: Fourier transform infrared spectra of optimized formulation

Table 4: FTIR spectrum of Optimized Formulation

Sl.No	Standard Value(cm^{-1})	Observation(cm^{-1})	Interpretations
1	3393.39-2489.54	2917.28	C-H Bending
2	2622.76-1631.04	1738	Ketones Stretching
3	1128.69-1051.01	1051.87	Alkyl Ketone Bending
4	1051.01-712.55	875.8	OH Bending

The standard graph results were shown in table 3. From the graph (Figure 3). From the graph we can say that Beer and Lamberts law is obeyed between 0 and 50µg/ml concentrations. The straight line is seen with r^2 value of 0.9972 [Figure 3].

Table 5: Calibration curve of ITOPRIDE HCl in 7.4 Phosphate Buffer

Concentration(µg/ml)	Absorbance(nm)
1	0.722
2	1.353
3	1.863
4	2.562
5	3.253

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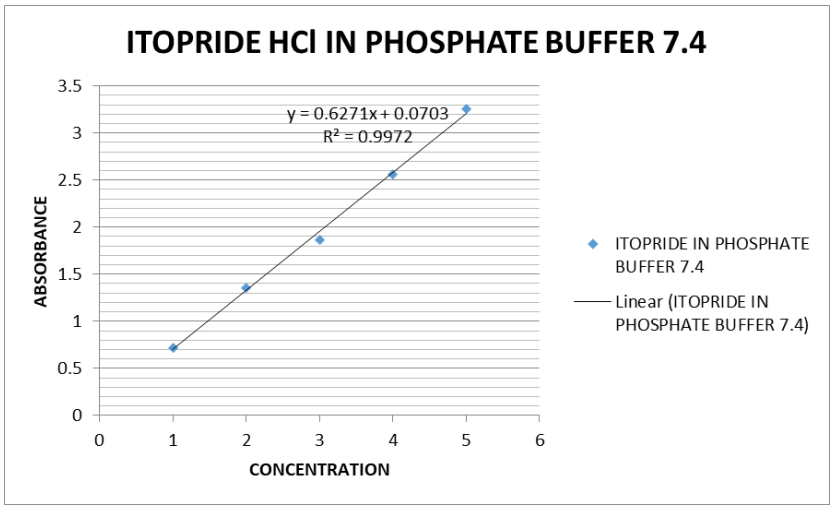

Figure 3: Calibration curve of ITOPRIDE HCl in Phosphate Buffer 7.4

All the pre compression evaluation values were shown in table 4. Bulk density and tapped density values of prepared blends were in between 0.59-0.63 g/ml, 0.73-0.76 g/ml respectively. The angle of repose of powder blends values were found between 30°88´-36°50´. Compressibility index values were found between 7.01%-7.59%. Hausner`s ratio values were found between 1.06-1.24. From these values, it was found that all the powder had good flow properties, results were shown in Table 6.

Table 6: Pre compression Evaluation

Formulation	Bulk Density(g/ml)	Tapped density(g/ml)	%compressibility	Hausner`s ratio	Angle of repose
F1	0.620±0.12	0.769±0.76	7.59±0.032	1.24±0.032	26°50´±0.025
F2	0.623±0.24	0.767±0.72	7.57±0.014	1.23±0.014	25°37´±0.041
F3	0.634±0.09	0.764±0.64	7.54±0.021	1.20±0.021	24°30´±0.068
F4	0.636±0.08	0.760±0.43	7.53±0.061	1.19±0.061	23°30´±0.054
F5	0.638±0.21	0.755±0.22	7.45±0.059	1.08±0.059	22°49´±0.062
F6	0.612±0.16	0.751±0.21	7.41±0.043	1.02±0.043	21°72´±0.071
F7	0.608±0.15	0.748±0.18	7.32±0.081	1.06±0.081	25°38´±0.053
F8	0.600±0.23	0.744±0.24	7.22±0.034	1.06±0.034	23°84´±0.075
F9	0.595±0.18	0.736±0.66	7.12±0.026	1.06±0.026	20°88´±0.086
F10	0.592±0.21	0.732±0.13	7.01±0.021	1.06±0.021	21°87´±0.042

All the post compression evaluation values were shown in table 5. The average hardness of medicated chewing gum was found between 3.0-4.0 kg/cm^2. Average weight of prepared medicated chewing gum was found in between 1022-1282 mg. Friability values were in between range of 0.56- 0.75%, and drug content of all formulations were found to be in between 91.38%-97.56% which is satisfactory, results were shown in Table 7.

Table 7: Post compression Evaluation

Formulation	Weight variation(mg)	Friability(%)	Hardness (kg/cm^2)	Thickness (mm)	Drug content(%)
F1	1022±2.18	0.56±0.06	3.5±0.72	5.17±0.048	95.12±0.22
F2	1062±6.80	0.74±0.03	3.0±0.36	5.17±0.048	92.51±0.24
F3	1082±4.19	0.84±0.04	3.0±0.59	5.18±0.042	93.55±0.24
F4	1102±4.28	0.76±0.02	3.5±0.24	5.17±0048	91.36±0.14
F5	1116±4.0.	0.78±0.02	3.5±0.43	5.18±0.042	96.56±0.12
F6	1136±4.91	0.83±0.05	3.0±0.30	5.18±0.048	92.14±0.05
F7	1182±4.57	0.85±0.02	4.0±0.14	5.17±0.048	93.56±0.20
F8	1212±5.32	0.68±0.07	4.0±0.32	5.18±0.042	92.19±0.04
F9	1232±7.58	0.71±0.07	3.5±0.24	5.18±0.042	94.56±0.25
F10	1282±8.62	0.75±0.06	4.0±0.14	5.17±0.048	94.24±0.01

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All the formulations prepared by direct compression mould method are grey colour, soft in nature, good consistency, no stickiness was found, results were shown in Table 8. and drug content of all formulations were found to be in between 91.38%-96.56% which is satisfactory, results were shown in Table 7.

Table 8 : General Evaluation

Formulation	Colour	Texture	Appearance	Stickiness
F1	Grey	Solid mass	Hard	Non sticky
F2	Grey	Good	Soft	Non sticky
F3	Grey	Good	Soft	Non sticky
F4	Grey	Sticky	Soft	Sticky
F5	Grey	Solid mass	Hard	Non sticky
F6	Grey	Good	Soft	Non sticky
F7	Grey	Good	Soft	Non sticky
F8	Grey	Good	Soft	Non sticky
F9	Grey	Good	Soft	Non sticky
F10	Grey	Good	Soft	Non sticky

The percentage in vitro drug release of formulations prepared by direct compression mould method are shown in table 9 and table 10 respectively. Formulation F5 shown 97.62% of drug release in 30 min. The comparative results of F1 to F5 and F6 to F10 results were shown in Figure 4 and Figure 5 respectively.

Table 9: Cumulative percentage of drug release profiles of formulations (F1-F5)

Time(min)	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	26.12	29.37	32.23	36.57	38.79
10	37.12	42.15	46.14	49.51	53.24
15	45.67	51.16	56.20	60.23	65.18
20	58.23	62.18	67.23	69.17	70.28
25	65.19	71.15	76.13	78.35	81.76
30	73.34	80.38	85.12	87.19	97.15

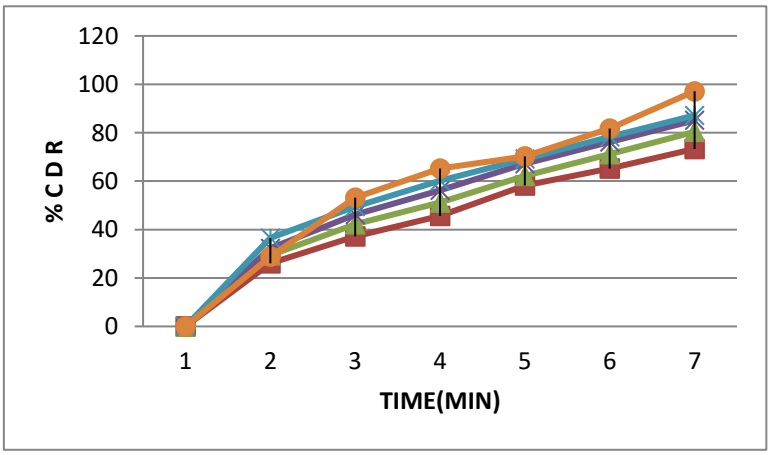

Figure 4: Cumulative percentage drug release profiles of formulations (F1-F5)

Table 10: Cumulative drug release of profiles of formulation (F6-F10)

Time(min)	F6	F7	F8	F9	F10
0	0	0	0	0	0
5	25.31	28.89	31.56	37.12	39.45
10	32.56	37.65	45.23	50.23	57.23
15	43.56	44.23	51.23	60.89	69.75
20	58.98	63.82	68.56	70.15	81.34
25	66.12	70.25	78.31	81.34	90.67
30	72.74	79.63	86.23	87.95	98.85

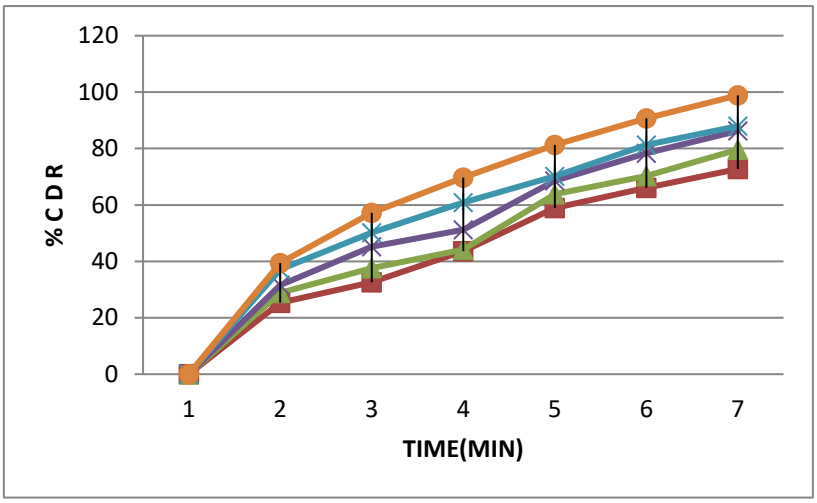

Figure 5: Cumulative percentage drug release profiles of formulations (F6-F10)

CONCLUSION

The present research aimed to fabricate a medicated chewing gum for treating motion sickness. The result of this study showed that chewing gum could be a very suitable form for buccal drug delivery of ITOPRIDE HCl. The formulation F5 had the best organoleptic properties and had a best drug release within prescribed time. The chewing gum prepared by the direct compression mould method. Evaluation was carried out of the formulated batches along with the stability studies showing satisfactory results. The formulation of ITOPRIDE HCl into medicated chewing gum was done successfully.

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