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Formulation & *In-vitro* evaluation of Domperidone soft chew

Ruheena Taranum and Sirisha Mittapally

Abstract
Soft chews are popular in recent times due to increased patient acceptance as it include candy base with sweet taste. It is patient friendly dosage form for paediatric & dysphagic patients. Soft chews have been exploited for delivery of calcium & vitamin supplements to patients with vitamin deficiency & hypocalcaemia. In the present research work Domperidone soft chews were formulated in order to increase patient acceptance, faster onset of action & for quick relief from nausea & vomiting compared to conventional dosage forms due to chewing effect drug is immediately released in saliva & most of it is absorbed in systemic circulation. Solubility of Domperidone was enhanced by complexation with cyclodextrins. Soft chew is prepared from sucrose, liquid glucose, milk cream, inter esterified vegetable fat & soya lecithin by heating & congealing method. It is evaluated for appearance, weight variation, drug content, & dissolution. The optimized formulation showed a drug release of 95.8% in 25mins using simulation method. Stability study was carried out at 30º±2ºC/65% RH± 5% for 3months & has shown satisfactory result.

Keywords: Soft chews, Domperidone, nausea & vomiting, heating & congealing

1. Introduction
Soft chews are novel drug delivery system. It can be administered easily without water, can be used for local or systemic action & enhances bioavailability due to rapid absorption. Soft chews are sweet in taste because of its tasty candy clothing & can be used for incorporating bitter drugs like aspirin, erythromycin, cimetidine; hence soft chew dosage form can also serve as better alternative for taste masking. It is also visually appealing thereby it generates interest among children & people of other age group who are disinterested in taking medicine or vitamin supplement. It makes consumption easy without the need to force or remind them. It can also used by individuals having difficulty.

Various novel formulations include chewing gums, orally disintegrating strips & soft chews. There are soft chews of plant stanol ester used to lower cholesterol, multivitamin & calcium soft chew used to overcome vitamin deficiency & hypocalcaemia. Soft chews have also established its importance in veterinary science. Animals find it difficult to swallow hard tablets, capsules. Chewing becomes unpleasant to animals due to grittiness of chewable tablets & bitter taste of drugs. Hence soft chew serves as better alternative to them as consumption becomes easy due to its soft nature [1].

Soft chew includes sweetener, texturizer & emulsifying agent. Generally sucrose is used as sweetening agent, but dextrose or maltose can also be used in combination to balance taste and to decrease sweetening power of sucrose to certain extent. When used in confection sucrose crystallize easily leading to graining effect, hence it can be avoided using liquid glucose which prevents crystallization. Different types of Sugar Systems like combination of various syrups i.e., corn Syrup; glucose Syrup; invert Syrup; high fructose syrup; with sugar (Sucrose, fructose; maltose; trehalose) can be used to change the texture of soft chew. Sugar free soft chews can also be prepared using bulk sweeteners like mannitol, isomalt & sorbitol but it has less sweetening property & in order to make it palatable it can used in combination with artificial sweeteners like aspartame, cyclamate & acesulfame K. Fats are also incorporated in it in order to improve mouth feel, aid in mastication & to get rid of stickiness [2].

Nausea and vomiting are manifestation of various pathophysiological condition like motion sickness, pregnancy, cancer, and postoperative conditions. Nausea refers to the sensation of discomfort /uneasiness in the upper stomach which may or may not lead to vomiting. Vomiting is defined as to forceful oral expulsion of the gastric contents and the proximal small intestine due to contraction of abdominal or chest wall musculature.

Antiemetic drugs blocks receptors like H1 histaminic, dopamine D2, 5-HT3 receptor, muscarinic, and neurokinin1 (NK1) receptor there by preventing or suppressing vomiting. Mechanism of action of Anticholinergic, H1-antihistamines, Neuroleptics, 5-HT3 antagonists involves penetration through blood brain barrier leading to sedation. Antiemetic like Domperidone, metoclopramide, act by blocking D2 receptors in the chemoreceptor trigger zone. Metoclopramide has more side effects than Domperidone. Gastro kinetic drugs like metoclopramide and Domperidone does not cause any side effects related to brain since the Chemoreceptor Trigger Zone (CTZ) is present outside the blood brain barrier [3]

There is need for reformulation of existing drugs into novel drug delivery systems (NDDS) in order to distinguish from future generics competition in the market. Formulation of soft chews will provide therapeutic effect within few minutes resulting in fast relief from symptoms of nausea & vomiting. It will aid children & adults suffering from motion sickness & can be taken at any time & place easily hence it is more acceptable than other conventional dosage forms. In the present study complexation of Domperidone with cyclodextrins is done in order to enhance solubility as well as taste [4].

2. Materials & Methods

Table 1: Table showing list of materials with manufacturer

S. NO.	Name Of The Material	Manufacturer
1	Domperidone	B. Sharda Pharma Chem Ltd, Gujarat
2	Sucrose	SD-fine chemicals, Mumbai.
3	Liquid glucose	Baker's ville India Pvt. Ltd, Indore.
4	Liquid soya lecithin	Baker's ville India Pvt. Ltd, Indore.
5	Inter esterified vegetable fat	Baker's ville India Pvt. Ltd, Indore.
6	Milk cream	Amul India
7	Milk Solid	Nestle
8	Xantham gum	SD-fine chemicals, Mumbai.
9	Gelatin	SD-fine chemicals, Mumbai.
10	Sodium benzoate	Fischer Chemicals, Mumbai.
11	Sodium chloride	SD-fine chemicals, Mumbai.

2.1 Drug-Excipient Compatibility Studies

FTIR spectroscopy is an analytical technique used to find any interaction between the drug & excipients used in the formulation. About 1-2mg of Domperidone fine powder & 200-300mg of dry KB r powder were taken in agate mortar & grounded to fine particle size powder using pestle. Pellet was prepared & spectrum was recorded in the wavelength region of 4000-400cm^{-1} by FTIR spectrophotometer. The IR spectrum of the formulation was compared with the spectrum of pure drug to determine any possible drug-excipient interaction [5].

2.2 Formulation Development

1. Preparation of Domperidone cyclodextrins inclusion complex

Inclusion complexes of Domperidone with beta-cyclodextrins were prepared in different molar ratios, i.e. 1: 1, 1: 2, 1: 3 by kneading method as follows. First beta cyclodextrin was taken in a mortar & was wetted with alcohol until a paste was obtained then Domperidone was slowly added into the paste. Kneading was done manually for about an hour & during this period required amount of alcohol was added to maintain paste like consistency. The mixture was dried in an oven at 50°C for 24hr. Then the dried complex was powdered using mortar & pestle & passed through sieve no.65. Prepared inclusion complexes were stored in a dessicator [6, 7].

2. Preparation method of soft chew

Soft chew is prepared by heating & congealing method. Soft chew base containing sucrose, liquid glucose & milk cream is heated up to 120 °C then it is mixed with other excipients & allowed to congeal at room temperature. The detailed procedure for preparation of soft chew is mentioned in the following steps:

1. All ingredients are weighed accurately
2. First sugar & liquid glucose were taken & this mixture was heated at low temperature on a hot plate until it is dissolved.
3. Following that milk cream was added & the mixture was heated with stirring until it reaches 120 °C
4. Then the mixture is removed from heat & required amount of inter esterified vegetable fat, Liquid soya lecithin, & sodium chloride is added
5. Domperidone, tocopherol & sodium benzoate were added followed by colour, flavour & mixed thoroughly
6. It was transferred into mould & is allowed to cooled at room temperature until it becomes firm enough.[8]

Table 2: Formulation of Domperidone soft chew

S. No.	Ingredients(g)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Optimized Domperidone cyclodextrine complex	0.216	0.216	0.216	0.216	0.216	0.216	0.216	0.216	0.216
2	Sucrose	10	12	12	12	12	12	14	12	10
3	Liquid glucose	14	12	4	7	12	12	2	4	6
4	Milk solid	2	2	10	7	-	-	-	-	-
5	Xantham gum	-	-	-	-	2	-	-	-	-
6	Gelatine	-	-	-	-	-	2	-	-	-
7	Milk cream	-	-	-	-	-	-	10	10	10
8	Inter esterified vegetable fat	2	2	2	2	2	2	2	2	2
9	Liquid soya lecithin	1	1	1	1	1	1	1	1	1
10	Sodium chloride	0.38	0.38	0.38	0.38	0.38	0.38	0.38	0.38	0.38
11	Sodium benzoate	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
12	Tocopherol	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
	Total weight	30g	30g	30g	30g	30g	30g	30g	30g	30g

Each soft chew weighs 5g & contains 36mg of drug-βcyclodextrin complex

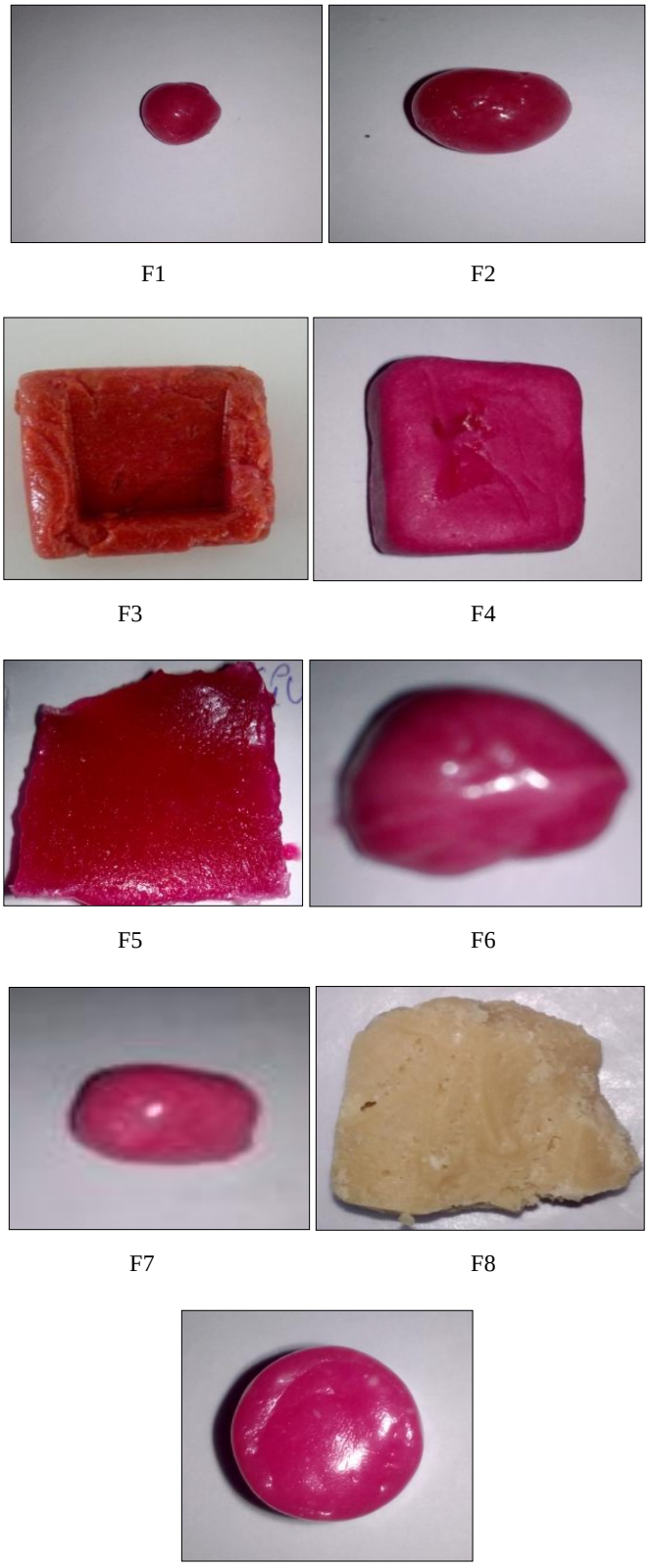

Fig 1: Different formulations of soft chew

3. Evaluation of Domperidone Betacyclodextrin Inclusion Complex

1. Solubility studies

Solubility studies of both pure drug & cyclodextrin inclusion complexes were carried out. Excess of pure drug & cyclodextrin inclusion complexes were added to volumetric flasks containing 20ml of distilled water & were shaken for 4hr at ambient temperature. Samples were filtered using what man filter paper, diluted appropriately & absorbance was taken at 284nm [9-12]

2. Dissolution studies

Dissolution studies were carried out using USP type II rotating paddle apparatus. Water was taken as dissolution medium which was maintained at 37± 0.5 °C. The paddle speed was adjusted to 100rpm. Pure drug (10mg) & inclusion complex equivalent to 10mg of drug was dispersed in basket containing water. About 5ml of sample were withdrawn at 10, 20, 30,40,50,60 minutes & replaced with equal volume to maintain sink conditions. Samples were filtered using what man filter paper, diluted appropriately, & absorbance was taken at 284nm [6].

3. Drug content

Drug content of complexes was determined by taking complex equivalent to 10mg of Domperidone in a volumetric flask & was dissolved in 20ml of 6.8 pH buffer using mechanical shaker & then volume was made up to 50ml. Then it was filtered & 1ml of filtrate was diluted to 10ml using buffer & absorbance of samples were determined at 284nm [13].

3.1 Evaluation of Domperidone Soft Chew

1. Physical appearance

Soft chew is evaluated for parameters like colour, odour, stickiness & texture. Initially colour of soft chew is noted then odour is evaluated whether it is pleasant or not. Stickiness is determined by rubbing the soft chew between two fingers. Texture is determined by pressing it between fingers to know whether it is hard or soft.

2. Weight variation

About twenty soft chews were taken & their individual weight was determined using analytical balance. Average weight &%weight variation was determined [8].

3. Drug content

Ten soft chews are taken & crushed in a mortar using pestle. Complex equivalent to 10 mg of Domperidone was taken & dissolved in 100ml of volumetric flask containing 6.8 pH buffer. Then the solution was filtered & 1ml of filtrate was diluted to 10ml with 6.8 pH buffer & absorbance was taken at 284nm using UV/Visible double beam spectrophotometer [3].

4. Dissolution

- Dissolution was carried using two different procedures
- In first procedure dissolution of soft chew was out carried out using USP II dissolution apparatus (paddle). 900ml of 1.2 pH buffer was taken as dissolution media which was maintained at 37± 0.5 °C & the paddle speed was adjusted to 50rpm. 5ml of sample were withdrawn at 5, 10,20,30,45 minutes & replaced with equal volume of fresh buffer. Samples were filtered, diluted & analyzed spectrophotometrically at 284nm.
- In second procedure, in order to simulate chewing action soft chew was suspended between disintegration beads & it was given munching effect in a beaker containing 30ml of 6.8 pH buffer using glass rods for 5mins during this period samples were withdrawn at 1,5 minutes & replaced with equal volume of fresh buffer. After 5 minutes then it was transferred into USP II dissolution apparatus containing 1.2pH buffer as dissolution medium

with paddle speed of 50rpm. Samples were withdrawn at 10,15,20,25 minutes replaced with equal volume of fresh buffer. Samples were filtered, diluted & analyzed spectrophotometrically at 284nm [14].

5. Stability studies

Stability studies of optimized formulation was carried out as per ICH guidelines at 30º±2ºC/65% RH± 5% for 3months & drug content of formulation was determined each month [15].

4 Results & Discussion

4.1 Drug Excipient Compatibility Studies

Compatibility studies were carried out using Shimadzu Fourier-transform infrared spectrophotometer. Major peaks of Domperidone were found at 800-600 cm^{-1} (C-Cl bending), 1700-1640 cm^{-1} (C=O stretching), 1200-1000 cm^{-1} (C-N stretching), 1500-1300 cm^{-1} (C-NH stretching). Major peaks of β cyclodextrine were found at 3389 cm^{-1} (OH symmetric), 2925 cm^{-1} (CH2 stretching), 1158 cm^{-1} (C-O-C stretching), 1027 cm^{-1} (O-H bending vibration). FTIR of the complex & formulation was carried out & there was no change in the functional groups. Hence the activity of Domperidone is retained in the formulations & is compatible with the formulation.

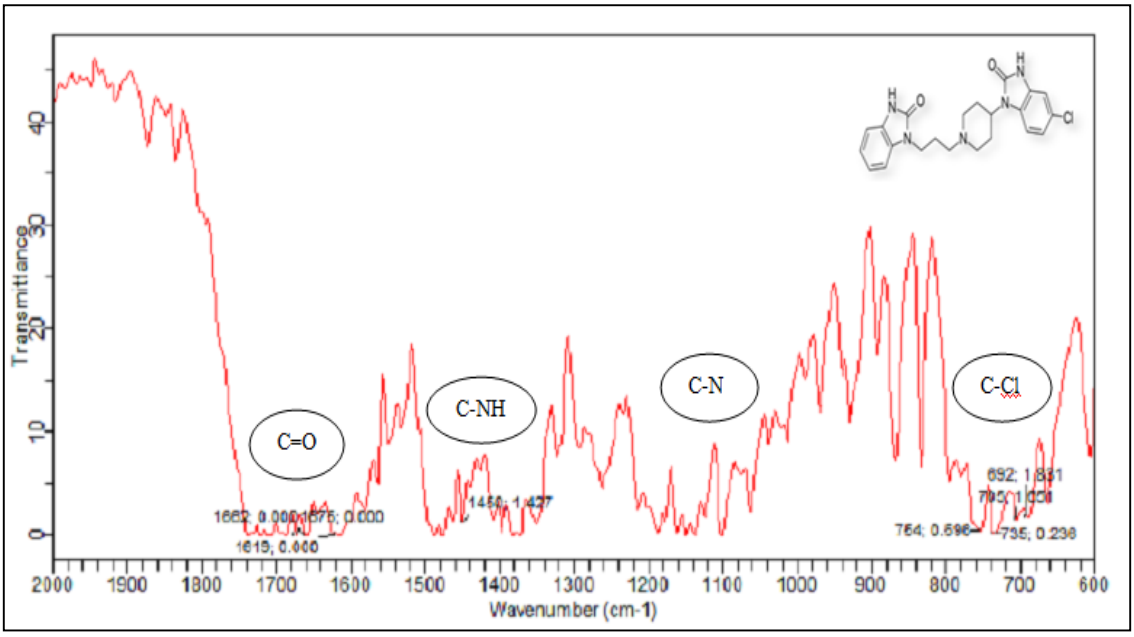

Fig 2: FTIR spectra of Domperidone

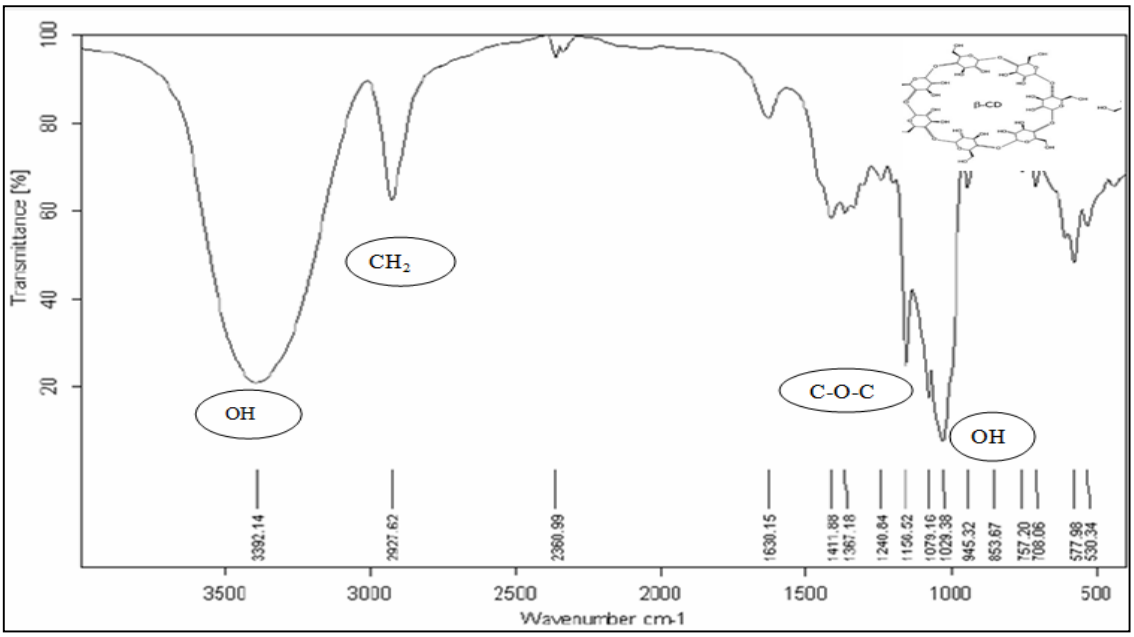

Fig 3: FTIR spectra of βcyclodextrin

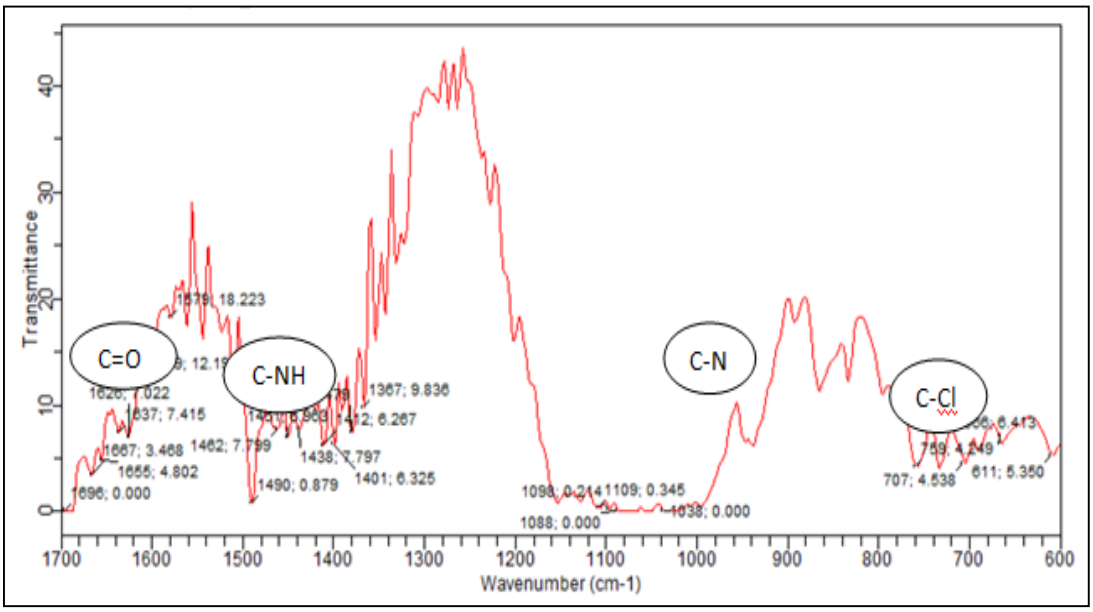

Fig 4: FTIR Spectra of drug & β cyclodextrin

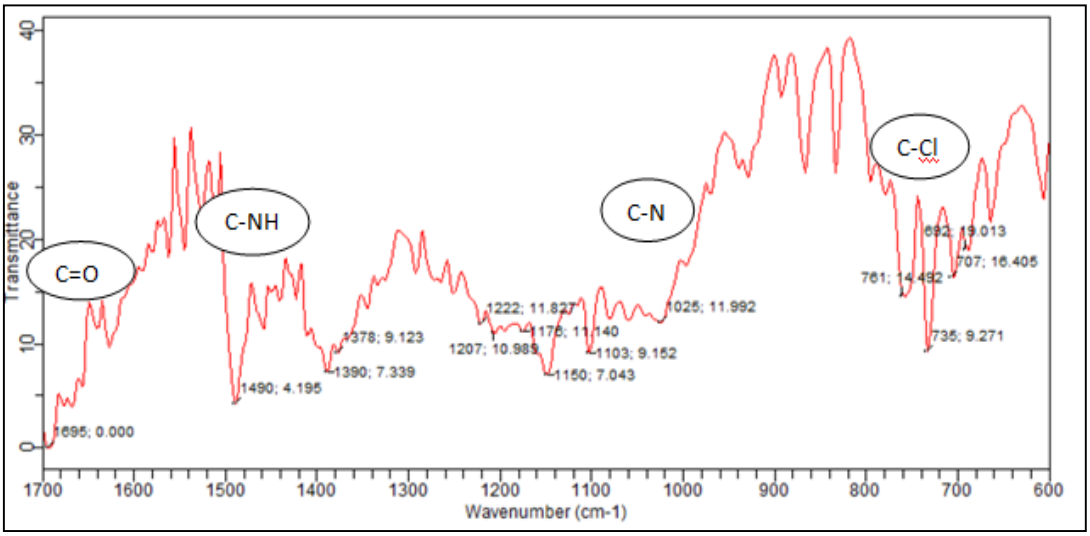

Fig 5: FTIR Spectra of optimized formulation F9

4.2 Solubility Studies

Solubility studies of complexes & pure drug was carried out & 1:1 ratio showed highest solubility of 0.98±0.015mg/ml.

Table 3: Solubility studies of Domperidone cyclodextrin inclusion complex

S. NO.	Drug & β Cyclodextrin	Solubility In Water (mg/ml) (n=3)
1	Pure drug	0.010±0.024
2	1:1 Complex	0.98±0.015
3	1:2 Complex	0.65±0.021
4	1:3 Complex	0.43±0.036

4.3 Drug Content

The drug content of various ratios of drug & cyclodextrin was determined.

Table 4: Drug content of Domperidone cyclodextrin inclusion

S. NO.	Drug & β Cyclodextrin	Drug Content (%) (n=3)
1	1:1 Complex	98±0.05
2	1:2 Complex	95±0.020
3	1:3 Complex	97±0.061

4.4 Dissolution Studies

Dissolution of complexes was carried out in distilled water & 1:1 complex showed a drug release of 80.57% in 60 minutes.

Table 5:%CDR of drug & complexes in water

Time (mins)	Pure Drug (%)	1:1 Complex (%)	1:2 Complex (%)	1:3 Complex (%)
10	9.05	35.24	28.40	21.17
20	13.54	45.15	38.32	32.45
30	27.02	54.36	47.30	41.50
40	31.56	64.38	58.5	53.22
50	40.58	72.64	64.38	62.36
60	49.64	80.57	76.10	70.65

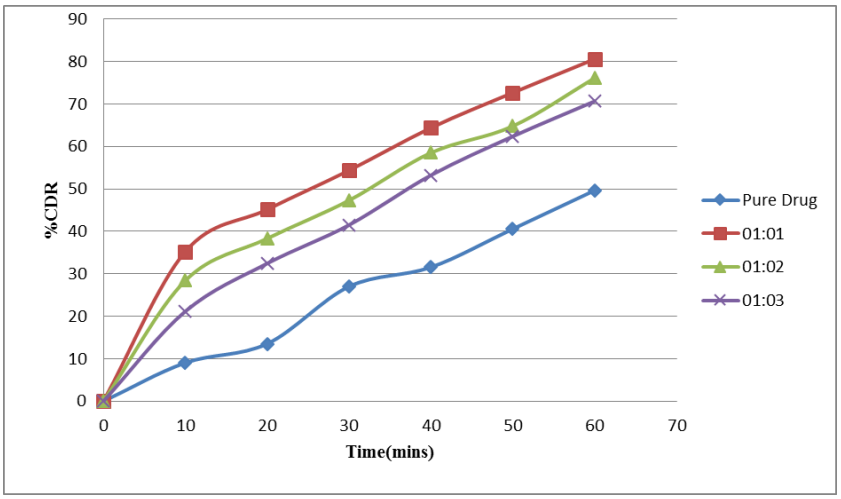

Fig 6: Dissolution studies of complexes

4.5 Evaluation of Domperidone Soft chew

1. Physical appearance

The optimized formulation (F9) was pink in colour, had pleasant odour, was non sticky & smooth in texture

Table 6: Physical appearance test parameters

S.NO	Test Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Colour	P	P	B	P	P	P	P	W	P
2	Odour	PL	PL	NP	PL	PL	PL	PL	PL	PL
3	Stickiness	S	S	NS	NS	S	S	NS	NS	NS
4	Texture	SS	SS	H	H	SS	SS	H	B	SS

P: Pink, B: Brown, PL: Pleasant, NP: Not pleasant, S: Sticky, NS: Non Sticky, SS: Smooth & Soft, H: Hard, B: Breakable

2. Weight variation

The optimized formulation showed a% weight variation of 0.3% which is within the limit i.e., ±5%.

Table 7: %Weight variation of soft chew

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation (%)	0.70±0.10	0.62±0.08	0.60±0.19	0.40±0.09	0.90±0.22	0.75±0.16	0.44±0.12	0.38±0.21	0.31±0.11

3. Drug content

Drug content of optimized formulation (F9) was found to be 96.51±0.40% in 6.8 pH buffer

4. Dissolution

The optimized formulation showed a drug release of 95.8% within 25 minutes using simulation method & a drug release of 93.9% in 45minutes using only dissolution apparatus.

Table 8: Dissolution studies of F9 formulation by simulation method

Time (mins)	%Cdr of Optimized Formulation F9
0	0
1	15.02
5	36.41
10	58.22
15	74.31
20	82.6
25	95.8

Table 9: Dissolution studies of F9 formulation using dissolution apparatus

time (mins)	%CDR of Optimized formulation F9
0	0
5	10.5
10	22.69
20	50.1
30	74.2
45	93.9

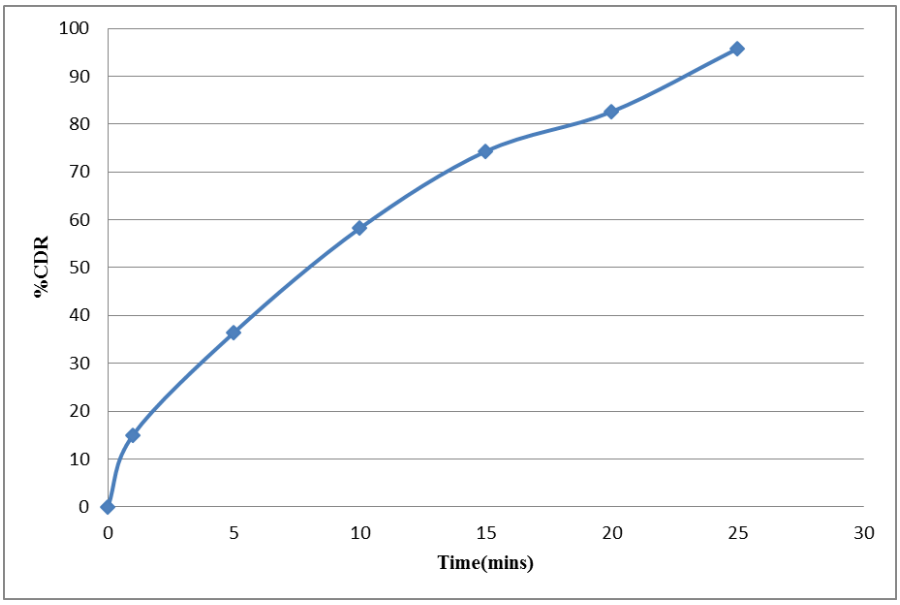

Fig 7: Dissolution studies of F9 formulation by simulation method

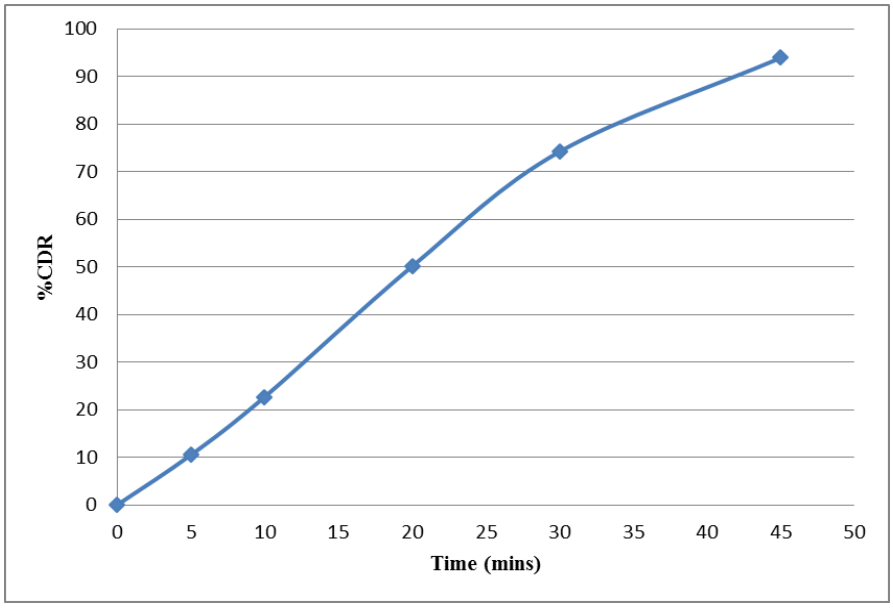

Fig 8: Dissolution studies of F9 formulation using dissolution apparatus

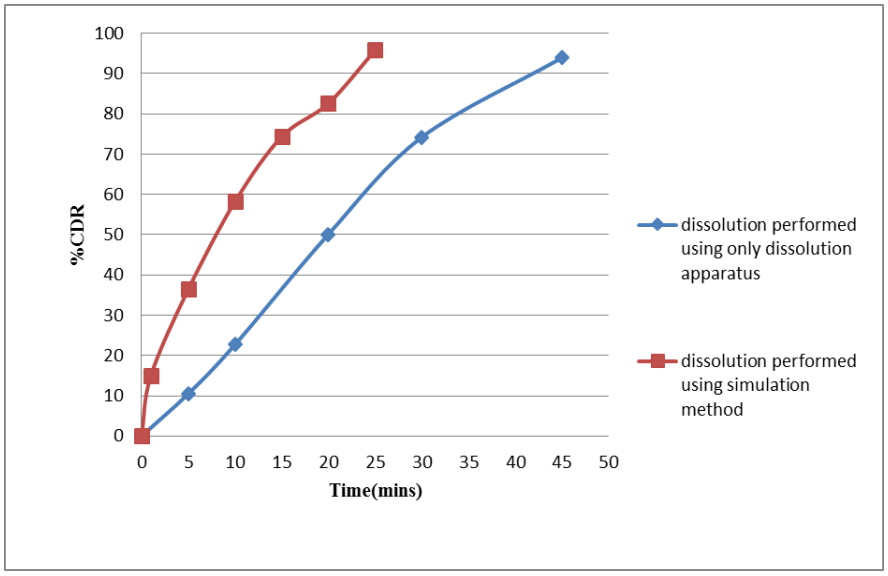

Fig 9: comparison of dissolution profile of F9 formulation using two different methods

5. Stability Studies

Optimized formulation F9 was wrapped in aluminium foil & was stored at 30º±2ºC/65% RH± 5%. It was found that there were no changes in appearance in whole duration of studies. Results of drug content is given in the following table

Table 10: Stability studies of optimized formulation

Stability Study Period	Drug Content (%) (n=3)
1 month	96.4±0.52
2 month	96.1±0.33
3 month	95±0.98

5. Conclusion

Medicated soft chew of Domperidone was formulated. Domperidone is BCS class II drug & it has less solubility in water so complexation with β cyclodextrin was done in 1:1, 1:2, 1:3 molar ratios. Solubility, dissolution studies were carried out in distilled water & optimized complex (1:1) showed a solubility of 0.98±0.015mg/ml & CDR of 80.57% in 60 mins. The drug content of optimized complex was found to be 98±0.05. Attempt was made to formulate soft chew using milk solid, xantham gum, gelatine, milk cream, but the optimized soft chew (F9) was obtained with milk cream with required amount of sugar & liquid glucose. Soft chew was evaluated physical appearance, weight variation, drug content & dissolution. Formulation had pleasant odour, & was soft unlike the other formulation which were hard & brittle. %weight variation was with in the limit i.e., ±5%. Drug content was found to be 96.5 ±0.40%. It showed a drug release of 95.8% in 25mins using simulation method & a drug release of 93.9% in 45minutes using dissolution apparatus. Optimized formulation was wrapped in aluminium foil & stored at 30º±2ºC/65% RH± 5% & during this period no significant change in drug content was observed.

6. References

1. Neil E. Paulsen. Process for manufacturing chewable dosage forms for drug delivery and products thereof.US 2008/0075759 A1, 2008.
2. Cristiana Soldani. Andrew Steven Whitehouse. Edible chewing gum and process for preparing. US 6,872,410 B2, 2005.
3. Mansi P, Balaram G. Formulation development and evaluation of medicated chewing gum of anti-emetic drug. Saudi Pharmaceutical Journal. 2016; 24:153-164.
4. Shivang A, Aliasgar F. Directly compressible medicated chewing gum formulation for quick relief from common cold. International Journal of Pharmaceutical Investigation. 2012; 2(3):123-133.
5. Nausheen S, Shahid M. Formulation & *in vitro* evaluation of meloxicam pulsin cap for pulsatile drug delivery. International journal of innovative pharmaceutical sciences & research. 2017; 5(08):126-138.
6. Gabriel Onn Kit Loh, Yvonne Tze Fung Tan, Kok-Khiang Peh**.** Enhancement of Norfloxacin solubility via inclusion complexation with β-cyclodextrin and its derivative hydroxypropyl-β-cyclodextrin. Asian journal of pharmaceutical sciences. 2016; 11:536-546.
7. Ghodke DS, Chaulang GM. Solid State Characterization of Domperidone: Hydroxypropyl-β-Cyclodextrin Inclusion Complex, Indian journal of pharmaceutical sciences. 2010; 72(2):245-249.
8. Mishra B, Sharma G. Investigation of organoleptic characteristics in the development of soft chews of calcium carbonate as mineral supplement. YAKUGAKU ZASSHI. 2009; 129(12):1537-1544
9. Pandit V, Gorantla R. Preparation and Characterization of Pioglitazone Cyclodextrin Inclusion Complexes. Journal of young pharmacists. 2011; 3(4):267-274
10. Chun-Hui Zhang, Bing-Xiang Zhao. A Novel Domperidone Hydrogel: Preparation, Characterization, Pharmacokinetic, and Pharmacodynamic Properties. Journal of drug delivery. 2011, 841054
11. Bruni G, Maietta M. Structure and properties of Domperidone and its succinate salt. Acta Crystallographica Section B: Structural Science. 2013; B69:362-370.
12. Sanghi DK, Rakesh tiwle. Phase solubility study of hydrophobic drug Domperidone using a novel technique inclusion complex with β-cyclodextrine. International journal of pharmaceutical research & analysis. 2014; 4:157-162.
13. Ghodke DS, Nakhat PD. Preparation and Characterization of Domperidone Inclusion complexes with cyclodextrin: Influence of preparation method. Iranian journal of pharmaceutical research. 2009; 8:145-151
14. Taranum R, Mittapally S. Soft chewable drug delivery system: oral medicated jelly and soft chew. Journal of Drug Delivery and Therapeutics. 2018; 8(4):65-72
15. Salunke T, Mayee R. Formulation and evaluation of medicated jelly of bitter drugs, International journal of research article pharmaceutical innovations. 2013; 3:1-14.