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Development And Evaluation Of Mouth Dissolving Tablet Using Domperidone

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Abstract:

In the present work, mouth dissolving tablets of domperidone were design with a view to enhance the patient compliance and provide a quick onset of action. Domperidone is antiemetic dopamine receptor antagonist and it has long half-life. The purpose of this study mouth dissolving tablets rapidly disintegrates in oral cavity and increase the dissolution so that the drug attains the therapeutic level in short time, so elicits better pharmacological effects. Mouth dissolving tablets prepared by direct compression and using super disintegrants like sodium starch glycolate, croscarmellose sodium and crospovidone in different concentration and evaluated for the pre-compression parameters such as bulk density, compressibility, angle of repose etc. The Mouth dissolving tabletformed was additionally found to be disintegrated within 1 min. The ratio of components in the Aqueous phase affected the thickness, drug content, tensile strength, percentage elongation, folding endurance, and release profile of Mouth dissolving tabletand the best results were obtained at DN2 formulation. Dissolution of prepared mouth dissolving tabletof Domperidone was performed using singhla apparatus in pH 6.8 phosphate buffer medium at 50 rpm with temperature being maintained at 37±0.5°C. The tabletprepared were evaluated for various parameters like thickness, weight variation, drug content uniformity, surface pH, folding endurance, disintegration time and in vitro drug release and were showed satisfactory results. The prepared batches of tablets were evaluated for hardness, weight variation, friability, drug content, disintegration time and in-vitro dissolution profile and found satisfactory. Among all, the formulation containing 5%w/w superdisintegrant crospovidone was considered to be best formulation, which release up to 98.15% in 15min.

Keywords: Mouth dissolving film, Domperidone, Superdisintegrants, Dissolution rate

INTRODUCTION

Mouth dissolving tablets disintegrate and/or dissolve rapidly in the saliva without the need for water, releasing the drug. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form[1]. Domperidone is selected as the model drug dopamine receptor

antagonist who comes under anti-emetic class6. Domperidone is optimized best suits for preparation of mouth dissolving tablets as it has longer half life and in case of vomiting it required quick release.[2] Among all the routes that have been investigated for the systemic delivery of pharmaceuticals via diverse pharmaceutical products of varied dose forms, oral drug delivery has been recognised for a decade as the most frequently used route administration. The oral route may have gained popularity due in part to its simplicity of administration as well as the conventional wisdom that the medicine is well absorbed when administered orally[3], just like the meals that are consumed on a regular basis. For paediatric, geriatric, bedridden, queasy, or noncompliant patients, recent technological advances have made it possible to administer medications in ways that are equally effective as the oral route.[4] Fast dissolving tablets can be prepared by various conventional methods like direct compression, wet granulation, moulding, spray drying, freeze drying and sublimation[5]. Direct compression one of the techniques requires the incorporation of a superdisintegrants into the formulation the use or highly water soluble excipients to achieve fast tablet disintegration. Direct compression does not require the use of water or heat during the formulation procedure and is the ideal method for moisture and heat-labile medications.[6] The aim of purpose work was to formulate and characterization mouth dissolving tablets of domperidone for rapid dissolution of drug and absorption, which may produce the rapid onset of action in the treatment of emetic.[7]

Material and Methods

Domperidone was obtained as a gift sample from Apex formulations, Chennai, India. Crospovidone and Lactose spray dried were gift sample from Signet Chemical Corporation, Mumbai. Croscarmellose sodium (Ac-Di-sol), Sodium starch glycolate (SSG) and Microcrystalline cellulose was gift samples from Sunrise Remedies, Ahmedabad, India. All chemicals and reagents used were of analytical grade.

Preparation of Domperidone Solution

Sample solutions were prepared by dissolving the Domperidone in demineralised water (Table). All samples were prepared in 10 mM KCl solution with target final Domperidone concentration of 32.44 ppm. The analytical procedure was performed for all the samples and repeated four times. All the samples were sonicated for 3 min using Ultrasonic bath. These were filtered using 0.22 micron Whatmann filter G4 and investigated by the electronic tongue system and analyzed using UV spectroscopy at 240 nm for Domperidone formulations. The mV readings obtained from first run was discarded as per requirement of Insent System (This ensures the conditioning of sensors). All the data obtained for each sample were treated statistically by in-built software in the system.

Table 1 Sample Preparation for Linearity Evaluation of Domperidone

Domperidone concentrations (ppm)	**Amount of Stock solution added ml**
2.88	1.2ml
12	5.0ml
60	25ml
120	50ml
180	75ml

Preparation of mouth dissolving tablets:

Domperidone mouth dissolving tablets were prepared by direct compression method. Different concentration of excipients was used to prepare different groups of mouth dissolving tablets. Compositions of various formulations are shown in Table 1. All the ingredients of the mouth dissolving tablets of domperidone were weighed and mixed in mortar with the help of pestle, then finally Aspartame,[8] 1mg Magnesium Sterate and 1mg was added material was slightly compressed on the 8mm flat-faced punch using a Rimek tablet press machine.[9] The total weight of the formulation was maintained 100mg.

Formulation Table 2.

INGREDIENT (mg)	**FORMULATION CODE**					
	F1	**F2**	**F 3**	**F 4**	**F 5**	**F 6**
Drug: complex Domperidone: Indion 204, (1:1)	20	20	20	20	20	20
Cross povidone	5	10	15	__	___	___
Croscarmellose sodium	__	___	___	5	10	15
MCC	60	55.45	61.95	60.00	55.00	50.05
Sodium Saccharin	10	10	10	10	10	10
Citric acid	0.5	0.05	0.05	0.05	0.05	0.05
Mg Stearate	3	3	3	3	3	3
Talc	2	2	2	2	2	2
Total weight (mg)	100	100	100	100	100	100

PREFORMULATION STUDY

Organoleptic properties [10]

The received sample of Domperidone was examined for its appearance, colour and odour.

UV Spectroscopy study: [11]

Domperidone was produced as a stock solution in phosphate buffer at pH 6.8, and its absorption maxima (λ max) were determined by measuring the UV spectrum of a 10 µg/ml solution

Calibration curve of Domperidone

With 10 ml of water, 10 mg of drug that had been precisely measured was dissolved. Domperidone solution of 20 g/ml was created from the principal stock solution using phosphate buffer solution. The range of this solution's scan was 200–400 nm.

RESULTS AND DISCUSSION:

Scanning of Domperidone by UV Spectrophotometry

The scanning of Domperidone was done as per the procedure described in methodology Section 4.3.

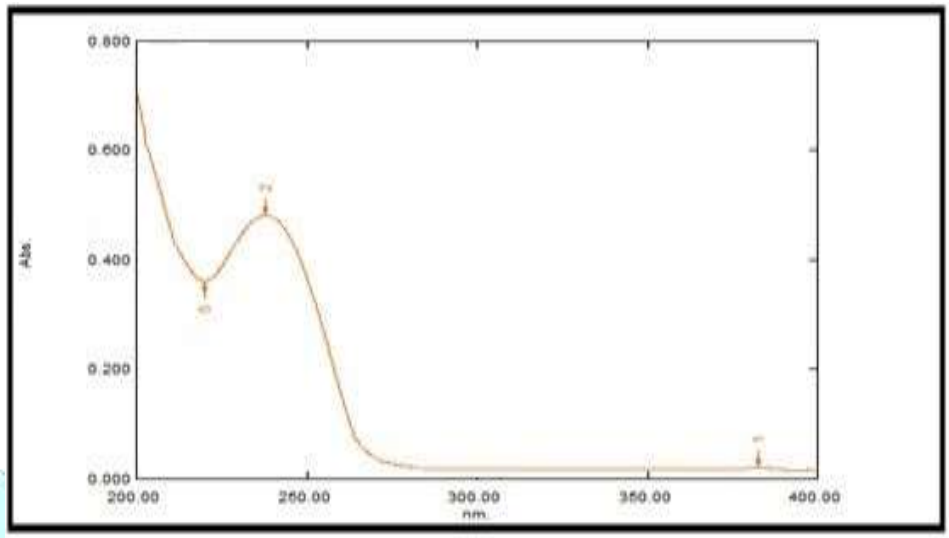


Figure 1: UV Spectra of Domperidone in 0.1 N HCl at 241nm

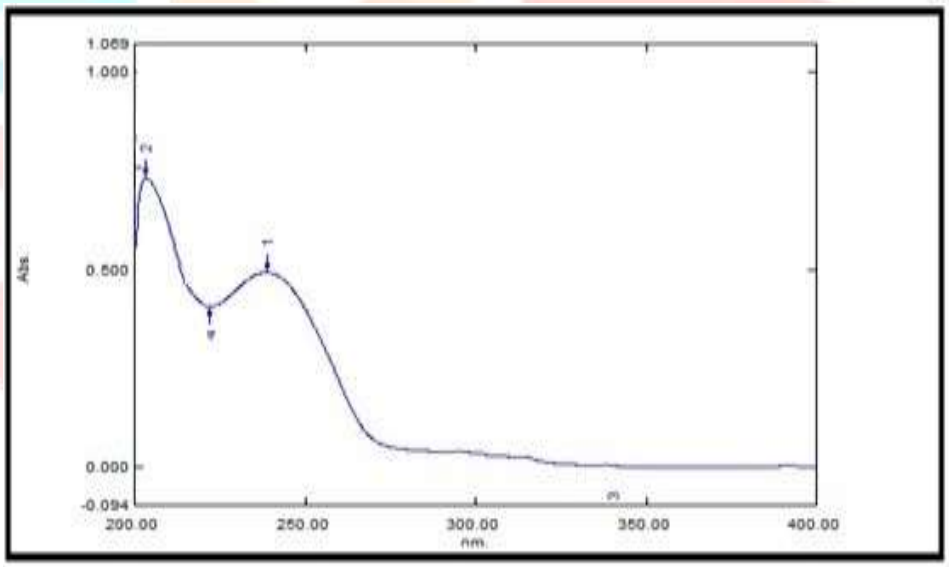


Figure 2: UV Spectra of Domperidone in methanol at 241nm

Calibration Curve of Domperidone by UV Spectrophotometry in 0.1 N HCl

Table . 3: Calibration Curve of Domperidone in 0.1 N HCl

CONCENTRATION (µg/ml)	ABSORBANCE (mean ± SD)
0	0.000 ± 0.000
2	0.102 ± 0.0032
4	0.162 ± 0.0005
6	0.251 ± 0.0040
8	0.327± 0.0015
10	0.410 ± 0.001
12	0.515 ± 0.002
14	0.581 ± 0.0015
16	0.642 ± 0.0015

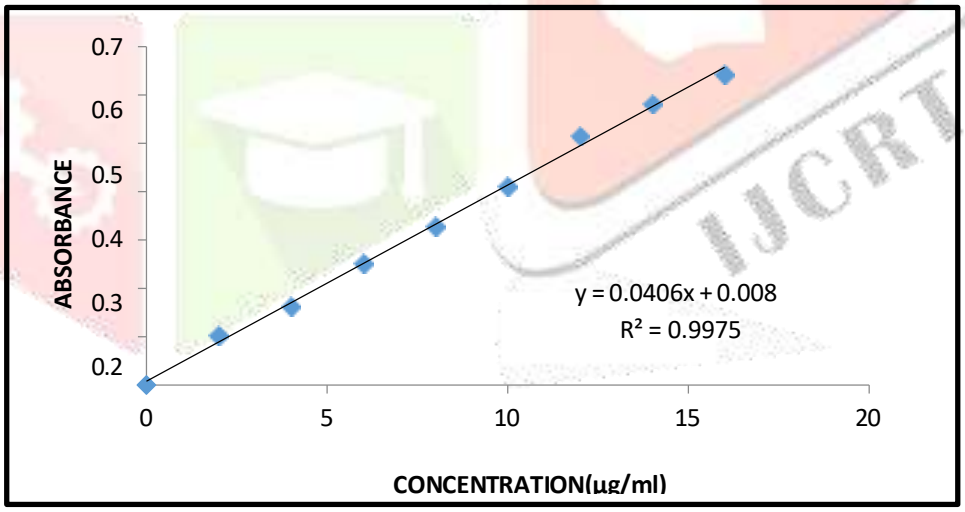


Figure . 3: Calibration curve of Domperidone in 0.1 N HCl

Characterisation of Drug and resins FTIR of Drug, Resins and Resinate

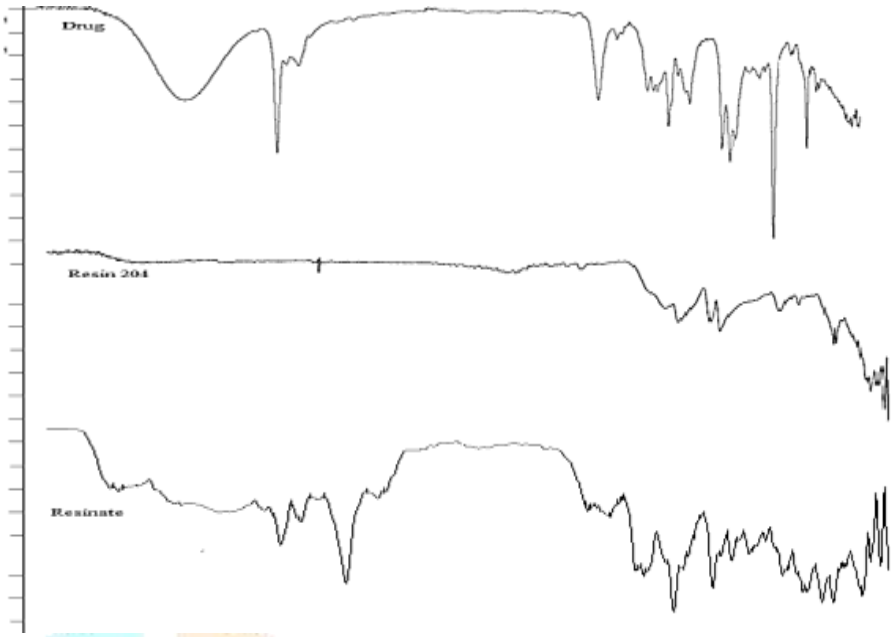


Figure. 4: FTIR spectra of Drug, Resin and Resinate

The interaction study between Domperidone and excipients in formulations were performed using FTIR spectrophotometer. The pellets were prepared on KBr press was introducing into FTIR spectra. The spectra were recorded over the wave number rang of 4000 to 400 cm^{-1}. The major IR peaks observed in Domperidone were 3325.64 (3300-3400) (N-H) stretching of 2˚-amine, 1705.73 (1665-2000) C=C, a peak at 1279 cm^{-1} representing C–N stretching of tertiary amine, 727.11 (600-800) cm^{-1} C-CL stretching in benzene ring. The absence of peaks at 1705 cm^{-1} and 1279 cm^{-1} in DRC confirms the complex formation of drug with resin. The peak at 3297.90 cm^{-1} in DRC corresponding to –OH stretching is also absent, which signifies that during DRC formation there is an interaction of the amino group of drug with the carboxylic group of the resin.

Differential Scanning Calorimetry (DSC)

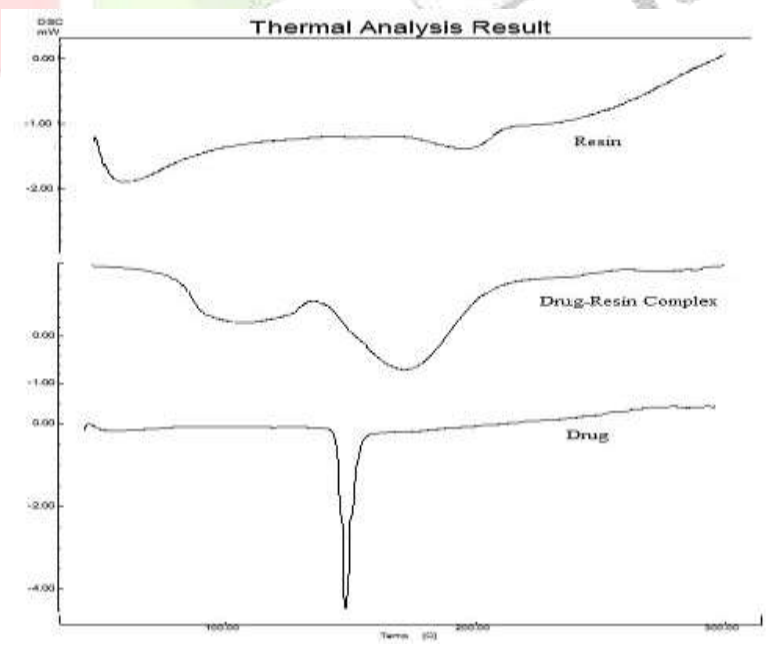


Figure 5: DSC thermogram of Drug, Resin and Resinate

Samples were analyzed by DSC using shimadzu corporation, Japan. The samples were placed into a pieced aluminium sample container. The studies were performed under static air atmosphere in the temperature range of 50 ℃- 250 ℃ at a heating rate of 10 ℃ per min. The peak temperatures were determined after calibration with a standard.

Optimization of Drug and polymer complex 1:1 ratio

The process of preparing the drug–polymer was optimized with respect to drug-to-polymer ratio, sorption time, pH, and temperature. Drug loading was carried out by the batch method using polymers Cross povidone, a drug–polymer ratio of 1:1 achieved equilibrium within 3 hours, resulting in 96.83% drug–polymer complex formation. The optimized drug–polymer ratio was evaluated at different pH values (4.2, 5, 6, 7, and 8). Maximum complex formation (90.73%) was observed at pH 7, indicating that drug–polymer complex formation was minimal in more acidic environments. The effect of temperature was studied at 30, 40, 50, and 60 ℃ using the optimized drug–polymer ratio and pH. The highest percentage of complex formation (98.56%) was obtained at 40 ℃, demonstrating that this temperature was optimal for drug loading compared to other studied conditions.

Table.4: Amount of Complexed Drug at Different Mixing Times

Drug: Polymer Ratio	Time(hrs.)	Free Drug (%)	Complexation Efficiency (%)
1:0.5	3	00.66	80.55
1:1	4	00.77	96.61

Evaluation of Drug–Polymer Complex

Table. 5: Evaluation Parameters of Drug–Polymer Complex

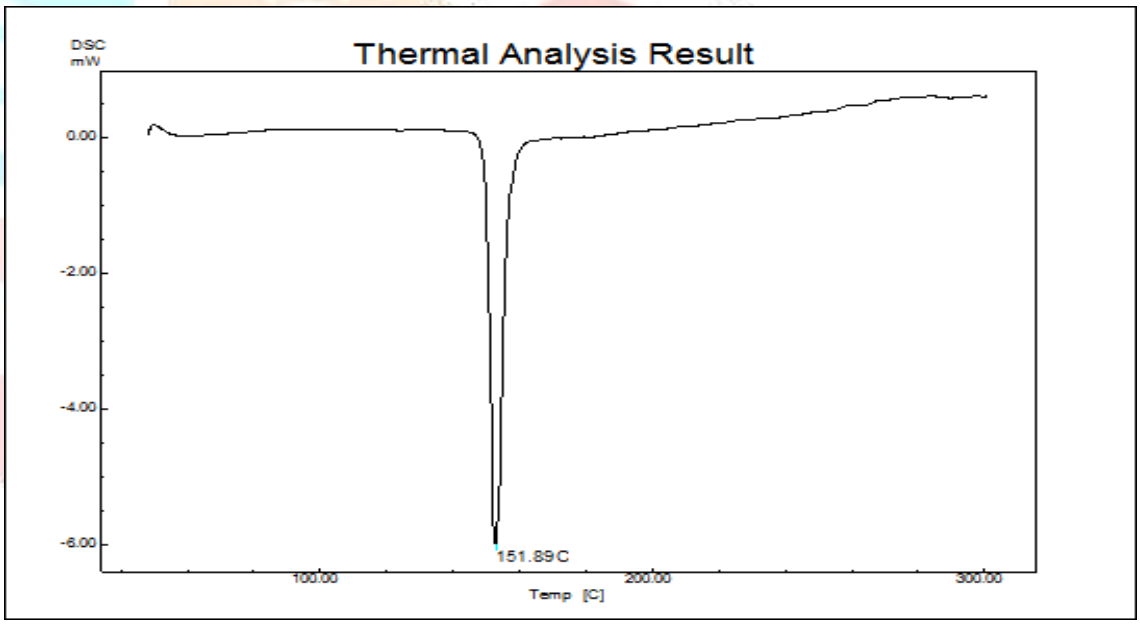
Sr.No.	Parameter	Result
1	%Yield	83.00%
2	Angle of repose	29.88±0.16°
3	Bulk density	0.43±0.024
4	Tapped density	0.48±0.012
5	Carr’s index	11.41±0.022
6	Hausner’s Ratio	1.20±0.015

Table. 6. FTIR study of Domperidone and polymers

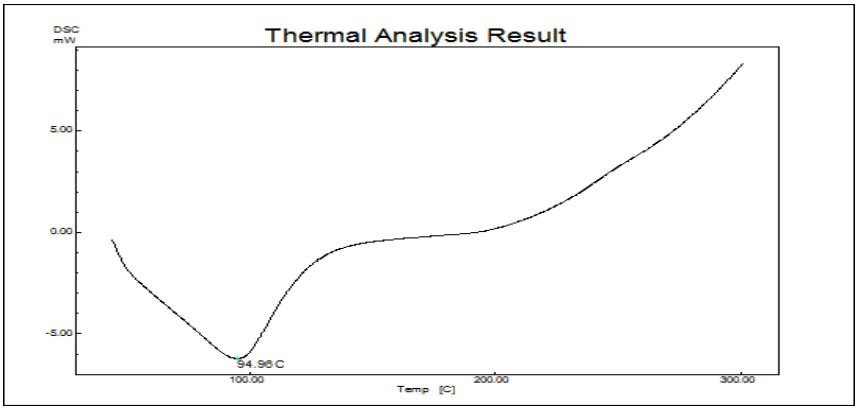
Drug& Excipient	Functional group	Peak (cm^{-1})	Mixture peak (cm^{-1})	Inference
Domperidone	2^0Amine	3345	3447	No Change
Croscarmellose sodium	Ether	1157	1153	No Change
	Methylene	1457	1458	
	Ether	1114	1108	
Crospovidone	Carbonyl group	1557	1556	No Change

DSC analysis of Domperidone formulation

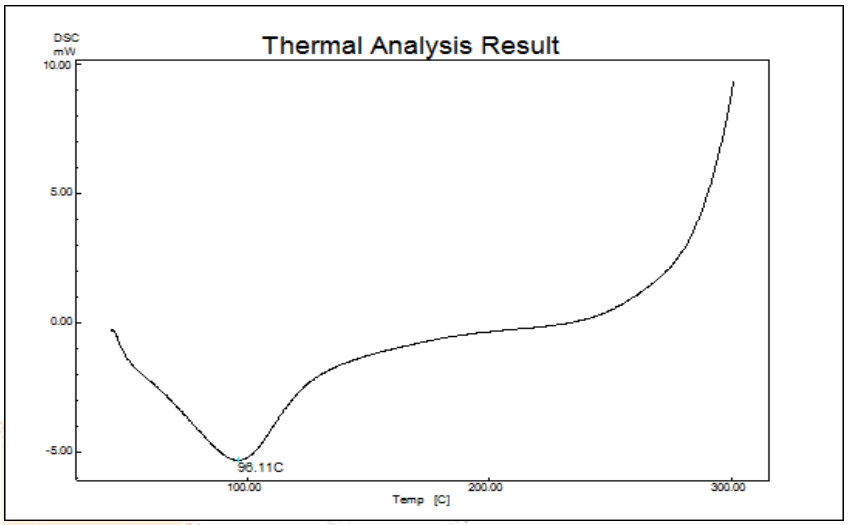
Domperidone Pure compound



Cross povidone



Croscarmolose



Final formulations

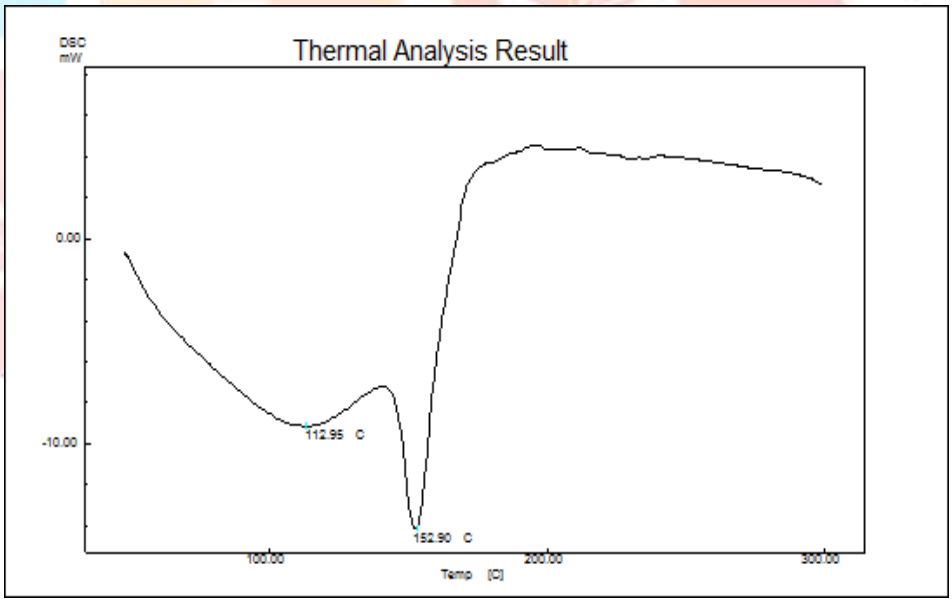


Figure 8: Thermogram of Drug and super disintegrants

Results of the DSC study of pure drug showed sharp endothermic peak at 151.89 ˚C. Similar endothermic peaks were obtained in the formulations at 152.90 ˚C clearly indicated that there was no drug polymer interaction. Results of DSC thermo grams were shown in the Figure 8.

Mouth dissolving tablet

Pre-formulation Studies

Table. 7: Melting point parameters

Drug	Parameter		
	Melting Point	Losson Drying	Partitions-coefficient
Domperidone	151^{o}C	0.31% w/w	3.4

Characterization of Mouth Dissolving Tablet

Determination of Weight Variation

Weight of Mouth Dissolving Dosage Form was measured as per the methodology given in The weight of Mouth Dissolving Dosage Form was found to be in the range of 98.00 and 84 mg The results of weights are as shown in Table 7.

Table. 7: Weight of Mouth Dissolving Dosage Form of Domperidone

	F1	F2	F3	F4	F5	F6
Weights in mg	98.00	97	95	93	87	84

In-vitro Disintegration Studies

The in vitro disintegration time of the mouth dissolving dosage form was measured according to the methodology described. The disintegration time was found to be in the range of 7.61 ± 0.48 seconds to 16.33 ± 0.58 seconds. The results of the disintegration study are presented in Table. 8.

Table. 8: Disintegration time of Mouth Dissolving Dosage Form of Domperidone

	F1	F2	F3	F4	F5	F6
DT in Sec	7.61	10.66	12.22	10.93	12.95	15.16

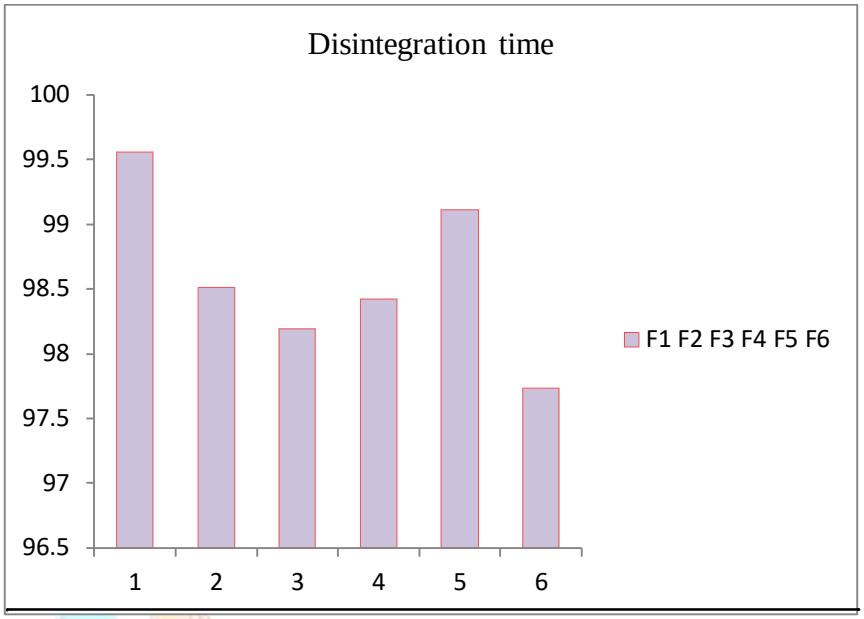


Figure 9: Disintegration time of M.D.T of Domperidone in optimized formula

As the concentration of the polymer increases the disintegration time also increases which results in delayed release of drug.

Measurement of Tensile Strength

Tensile strength of Mouth Dissolving Dosage Form was measured as per the methodology given in the tensile strength of Mouth Dissolving Dosage Form was found to be in the range of 51.72 ± 1.61 $N/m^2$and 75.66 ± 0.67 N/m^2. The results of tensile strength are as shown in Table 9.

Table. 9: Tensile Strength of Mouth Dissolving Dosage Form of Domperidone

	F1	F2	F3	F4	F5	F6
Tensile strength N/m^2	51.72	56.51	59.93	58.61	65.58	69.70

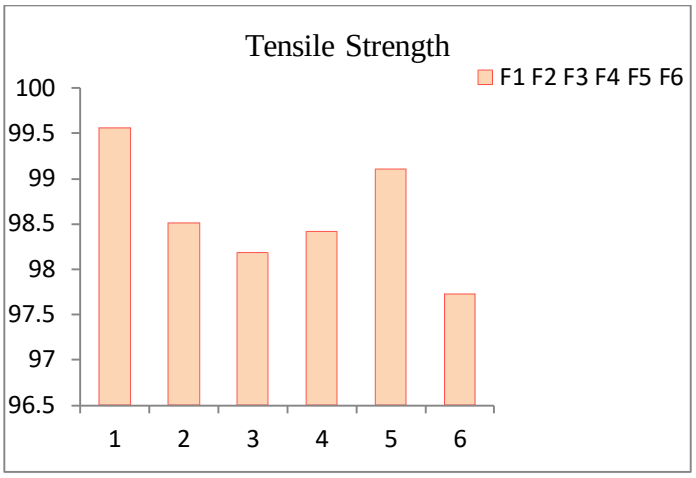


Figure 10: Tensile Strength of Domperidone Tablet

As the concentration of the polymer increases the tensile strength increases. It determines the strength and durability of the tablet.

Measurement of Percentage Elongation

Percentage Elongation of Mouth Dissolving Dosage Form was measured as per the methodology given in the Percentage Elongation of Mouth Dissolving Dosage Form was found to be in the range of 21.69±0.64 and 34.45± 0.88. The results of Percentage Elongation area shown in Table 10.

Table. 10: Percentage Elongation of Mouth Dissolving Dosage Form of Domperidone

	F1	F2	F3	F4	F5	F6
Percentage Elongation	34.45	32.52	29.66	30.08	27.84	24.86

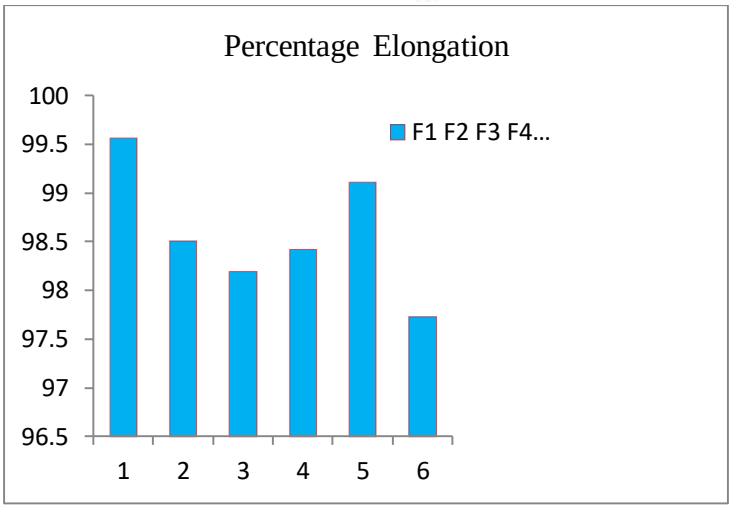


Figure 11: Percentage Elongation of Mouth Dissolving Dosage Form of Domperidone

As the concentration of the polymer increases the percentage elongation decreases. Percentage elongation helps to determine the elasticity of the tablet.

Determination of Drug Content

Drug content of Mouth Dissolving Dosage Form was measured as per the methodology given in the drug content of Mouth Dissolving Dosage Form was found to be in the range of 97.73±0.63 and 99.56±0.57 which was found within the acceptable limits as per IP. The results of drug content are as shown in Table 11.

Table. 11: Drug Content of Mouth Dissolving Dosage Form of Domperidone

	F1	F2	F3	F4	F5	F6
Drug content (%)	99.56	98.51	98.19	98.42	99.11	97.73

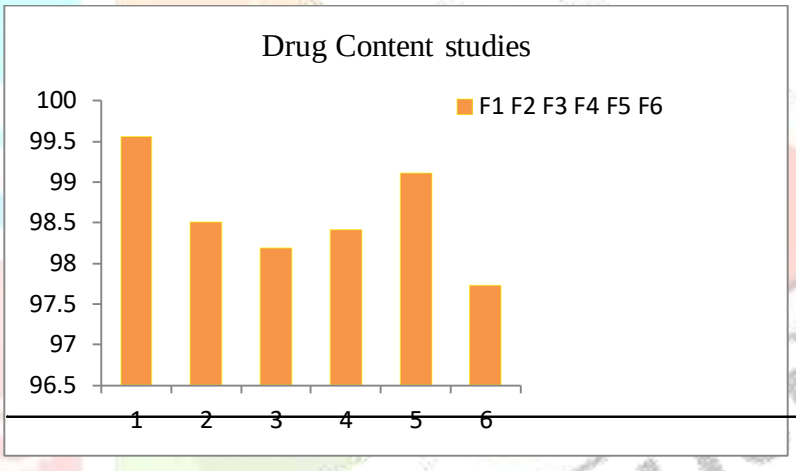


Figure 12: % Drug Content in Mouth Dissolving Tablet of Domperidone

As the concentration of the tablet increases the drug content decreases as the disintegration time is more. This parameter helps to identify the amount of drug present in the tablet.

In-vitro Dissolution Studies

The in vitro dissolution study of the mouth dissolving dosage form was carried out according to the methodology. The percentage cumulative drug release of all optimized formulations is illustrated in Figure 13 increased, the disintegration time, resulting in a corresponding decrease in the rate of drug dissolution. The percentage cumulative drug release data are presented in Table 12.

Table. 12 : In Vitro Dissolution Study of Mouth Dissolving Dosage Form of Domperidone

	F1	F2	F3	F4	F5	F6
% cumulative drug release	99.68	99.02	98.45	99.24	98.87	96.14

Table. 13: In Vitro Drug Release at Different Time Intervals

Time (Sec)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	80.94	77.67	75.81	78.32	76.54	72.79
4	83.13	80.45	79.65	82.04	80.07	76.86
6	85.52	82.95	81.06	84.14	81.98	79.62
8	88.24	86.09	85.69	86.68	85.92	81.66
10	91.05	90.23	89.72	90.75	89.91	87.93
15	94.91	94.02	73.13	94.45	93.67	91.25
20	97.82	97.06	96.32	97.43	96.76	94.8
25	98.75	98.14	97.54	98.37	97.93	95.67
30	99.68	99.02	98.45	99.24	98.87	96.14

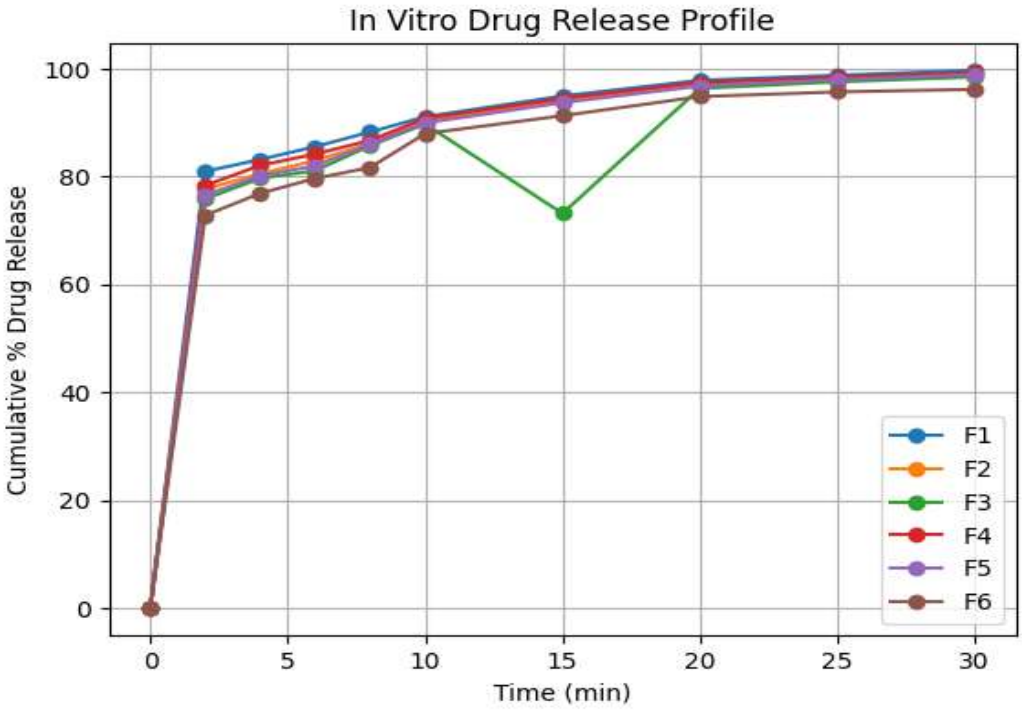


Figure 13: % Cumulative drug release of formulations F1 toF6

The in-vitro drug release profiles of formulations F1–F6 are shown in Figure 13. All formulations exhibited a rapid initial drug release followed by a gradual increase in cumulative percentage release. Among them, formulation F1 showed the highest drug release (99.68%) at 30 minutes, whereas F6 showed comparatively slower release. The results indicate effective drug diffusion from the formulations with slight variation depending on composition.

Surface pH

The surface pH of the mouth dissolving dosage form was measured according to the methodology. The surface pH of the mouth dissolving dosage form was found to be in the range of 6.97 ± 0.05 to 7.06 ± 0.12, indicating a near-neutral pH. The results of the surface pH study are presented in Table 14.

Table. 14: Surface pH of M. D. D. Form of Domperidone

	F1	F2	F3	F4	F5	F6
Surface pH	6.97	7.00	7.06	6.93	7.03	6.90

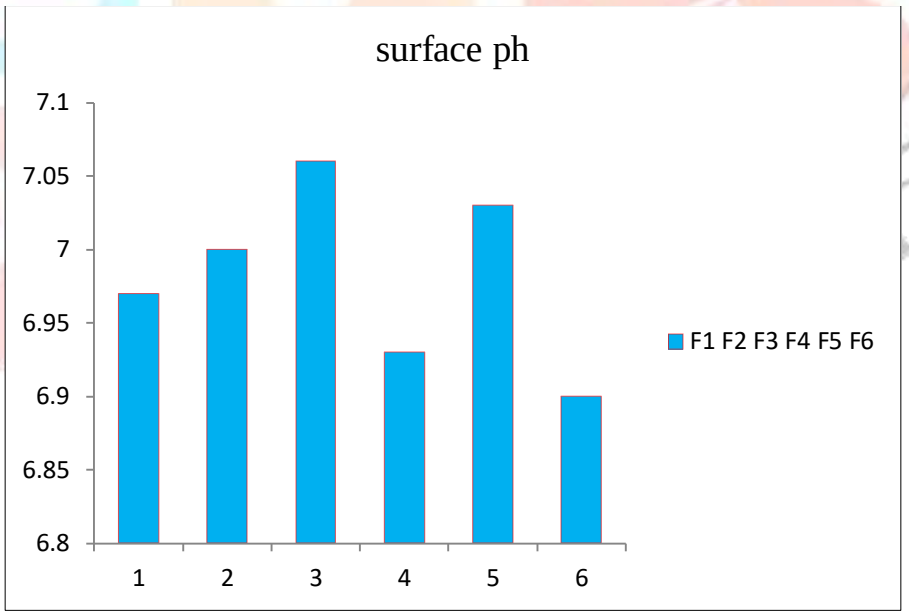


Figure 14: Drug Content in Mouth Dissolving Tablet of Domperidone (Optimized Formulation)

Stability study

Stability study was performed as per the procedure mentioned in methodology. Stability study results show that there was no significant change in disintegration time, drug content and in vitro drug release of the formulation. Table 15, 16 and 17.

Table 15: Stability Study Data for Disintegration Time

Stability study at 20°Cand 65%RH	
Test after time(days)	**Disintegration time (Sec.)**
0	7.6
15	8.1
30	8.6

Table 16: Stability Study Data for Drug content

Stability study at 30°C and 50% RH	
Test after time(days)	**%drug content**
0	99.56
15	99.14
30	98.63

Table 17: Stability Study Data for in-vitro studies

Stability study at 40°C and 75%RH	
Test after time(days)	**%Cumulative drug release after 30 Sec.**
0	99.68
15	98.42
30	97.33

DISCUSSION

In the present study particularly designed and developed mouth dissolving formulation Mouth dissolving tablet (MDT) immediate release of drug from the dosage form, to increase therapeutic efficacy and to improve patient compliance in case of allergy. Taste masked was done by batch method using Indion® 204; Complexes [1:1] were optimized by time, pH, and temperature and drug-resin proportion. These complexes were evaluated for angle of repose, bulk density, tapped density, Hausner's ratio, compressibility index and %yield. Taste masked done successfully by the resins indion-240. Optimum drug loading was fond to be at drug-resin ratio 1:1, pH was 7 and at 30°c temperature within 3 hr. time. Optimized complex was further used for preparing MDT. The tablets were prepared by using synthetic super disintegrant (CP and CCS) at different concentrations. The prepared tablets were evaluated for weight variation, hardness, Friability,

disintegration time, wetting time, water absorption ratio, drug content and in vitro dissolution tests. The tablets were subjected for stability study at 40°C/65% RH. The results clearly show synthetic super disintegrant were easily release drug within less few seconds. It was concluded that mouth dissolving tablet of domperidone could be successfully prepared using synthetic polymers. The in-vitro drug release profiles of formulations F1–F6 are shown in Figure 13. All formulations exhibited a rapid initial drug release followed by a gradual increase in cumulative percentage release. Among them, formulation **F1** showed the highest drug release **(99.68%)** at 30 sec, whereas F6 showed comparatively slower release. The results indicate effective drug diffusion from the formulations with slight variation depending on composition.

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