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FORMULATION AND EVALUATION OF ORAL DISINTEGRATING TABLETS OF DOMPERIDONE

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ABSTRACT

The aim of the present study was to develop formulation of domperidone to maintain constant therapeutic levels of the drug for over 30 minutes. In the present work, mouth dissolving tablets of domperidone was prepared by direct compression and effervescent methods. All the tablets were subjected to weight variation, drug content uniformity, hardness, friability, water absorption ratio, wetting time, *in vitro* dispersion time, dissolution, drug excipient interaction and short-term stability studies.

KEYWORDS: Domperidone, mannitol, magnesium stearate, aspartame.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reason that the oral route achieved such popularity may be attributed to its ease of administration as well as the traditional belief that by oral administration the drug is well absorbed as the food stuffs ingested daily. In fact, the development of pharmaceutical products for oral delivery, irrespective of physical form involves varying extents of optimization of dosage form within the inherent constraints of GI physiology. Therefore, a fundamental understanding of various disciplines, including GI physiology, pharmacokinetics, pharmacodynamics and formulation design are essential to achieve a systemic approach to the successful development of an oral dosage form. The more sophisticated a delivery system, the greater is the complexity of these

various disciplines involved in the design and optimization of the system. In any case, the scientific framework required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects:

a. Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug,
b. The anatomic and physiologic characteristics of the GIT, and
c. Physicochemical characteristics and the drug delivery mode of the dosage form to be designed.[1]

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules. Drinking water plays an important role in the swallowing of oral dosage forms.[2]

One important drawback of these dosage forms for some patients however is difficulty to swallow. Often times people experience inconvenience in swallowing conventional tablets and capsules, when water is not available, in case of motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic conditions and bronchitis.[3]

Many patients have difficulty swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy[4]. It has been reported that dysphagia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea.[5]

Because of the increase in the average human life span and the decline, with age, in swallowing ability, oral tablet administration to patients is a significant problem and has become the object of public attention. The problem can be resolved by the creation of rapidly dispersing or dissolving oral forms, which do not require water to aid swallowing. The dosage forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way.[4]

The orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, fast disintegrating tablets, porous tablets, rapimelts. However of all the above terms,

United States Pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European Pharmacopoeia has used the term "orodispersible tablet" for tablets that disperse readily and within three minutes before swallowing.

United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue". The disintegration time for ODTs generally ranges from several seconds to about a minute.[5]

Desired criteria for mouth dissolving drug delivery system

The tablets should

i) Not require water to swallow, but is should dissolve or disintegrate in the mouth in matter of seconds.
ii) Be compatible with taste masking.
iii) Be portable with taste masking.
iv) Have a pleasing mouth feel.
v) Leave minimal or no residue in the mouth after oral administration.
vi) Exhibit low sensitivity to environmental conditions as humidity and temperature.
vii) Allow the manufacture of tablet using conventional processing and packaging equipment at low cost.

Salient Features Of Mouth Dissolving Tablet

a) Ease of administration to patient who refuses to swallow tablets, such as pediatric, geriatric and psychiatric patients.
b) No need of water to swallow the dosage form, which is highly convenient feature for patients who are travelling and do not have immediate access to water.
c) Rapid dissolution and absorption of drug, which will produce quick onset of action.
d) Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, in such cases bioavailability of drugs is increased.
e) Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.

Formulation Aspects In Developing Odt

Orally disintegrating tablets are formulated by utilizing several processes, which differ in their methodologies and the ODTs formed vary in various properties such as

a) Mehanical strength of tablets
b) Taste and mouth feel
c) Swallowability
d) Drug dissolution in saliva
e) Bioavailability
f) Stability

The major advantages with effervescent formulation approach that it is a well established, easy to implement and mask the bitter taste of drug.[9] The effervescent system is generally composed of dry acid and dry base, which when react facilitate a mild effervescent reaction when the tablet contacts saliva. The effervescent reaction accelerates the disintegration of tablet through the release of carbon dioxide, water and salt. Due to evolution of carbon dioxide, the bitter taste of drug is also masked and a pleasant mouth feel is felt.

Direct compression is the easiest method to manufacture mouth dissolving tablets (MDTs). The great advantage of direct compression is its low manufacturing cost. It uses conventional equipment, commonly available excipients and a limited number of processing steps. In many cases the disintegrants used have a major role in the disintegration and dissolution process of fast disintegrating tablets made by direct compression method. The choice of a suitable type and an optimal amount of disintegrant is important for ensuring a high disintegration rate. The addition of other formulation components such as water-soluble excipients or effervescent agents can further enhance dissolution or disintegration properties.[10]

The various processes employed in formulating ODTs are as follows-

1. Freeze Drying Or Lyophilization

A process, in which water is sublimated from the product after freezing, is called freeze drying. Freeze-dried forms offer more rapid dissolution than other available solid products. The lyophilization process imparts glossy amorphous structure to the bulking agent and some times to the drug, thereby enhancing the dissolution characteristics of the formulation.

2. Molding

Tablets produced by molding are solid dispersions. Physical form of the drug in the tablets depends whether and to what extent, it dissolves in the molten carrier. The drug can exist as discrete particles or microparticles dispersed in the matrix. It can dissolve totally in the molten carrier to form solid solution or dissolve partially in the molten carrier and the remaining particles stay undissolved and dispersed in the matrix. Disintegration time, drug dissolution rate and mouth feel will depend on the type of dispersion or dissolution.

3. Cotton Candy Process

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy flos matrix is then milled and blended with active ingredients and exipients and subsequently compressed to ODT.

4. Spray Drying

Spray drying is a process by which highly porous, fine powders can be produced. The composition contains a bulking agent (mannitol and lactose), a disintegrant (sodium starch glycolate and croscarmellose sodium), an acidic ingredient (citric acid) and/ or alkaline ingredients (sodium bicarbonate), which when compressed into tablets show fast disintegration and enhanced dissolution.

5. Mass Extrusion

This technology involves softening the active blend using the solvent, mixture of water soluble polyethylene glycol using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product and cutting into even segments upon heated blade to form tablets.

6. Sublimation

This method includes the addition of a sublime salt to the tableting components, compressing the blend and removing the salt by the process of sublimation. The active ingredient, a diluent, a sublime salt (camphor/ ammonium bicarbonate), a binder and other excipients are blended and tablets are prepared. The tablets dissolve within 10-20 seconds and exhibit sufficient mechanical strength.

7. Sugar Based Excipient

Sorbitol, mannitol, dextrose, xylitol, fructose, maltose and polydextrose have been used as bulking agents. Because of their high aqueous solubility and sweetness, which impart a pleasing mouth feel and good taste masking, nearly all formulations for rapidly dissolving tablets contain sugar-based materials.

8. Direct Compression

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Directly compressed tablets disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agents. Disintegrant efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually required. As a consequence, products with optimal disintegration properties often have medium to small size and /or high friability and low hardness. Breakage of tablet edges during handling and tablet rupture during the opening of blister alveolus, all result from insufficient physical resistance. Disintegrants have major role in the disintegration and dissolution process of mouth dissolving tablets made by direct compression. To ensure a high disintegration rate, choice of suitable type and an optimal amount of disintegrant is important. Other formulation components such as water soluble excipients or effervescent agents can further enhance dissolution or disintegration properties.

Patented Technologies

9. Zydis Technology

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast-dissolving carrier material. When zydis units are put into the mouth, the freeze dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many materials designed to achieve a number of objectives. To impart strength during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of zydis unit during freeze drying process or long-term storage. Zydis

products are packed in blister packs to protect the formulation from moisture in the environment.

10. Lyoc

Oil in water emulsion is prepared and placed directly into blister cavities followed by freeze-drying. Non-homogeneity during freeze drying is avoided by incorporating inert filler to increase the viscosity.

11. Quick Solv

This technology uses two solvents in formulating a matrix, which disintegrates instantly. Methodology includes dissolving matrix components in water and the solution or dispersion is frozen. Then dry the matrix by removing water using excess of alcohol (solvent extraction). Thus the product formed has uniform porosity and adequate strength for handling.

12. Nano-Crystal Technology

Nano-crystal technology includes lyophilization of colloidal dispersions of drug substances and water soluble ingredients filled into blister pockets. This method avoids manufacturing process such as granulation, blending and tableting, which is more advantageous for highly potent and hazardous drugs. As manufacturing losses are negligible, this process is useful for small quantities of drugs.

13. Flashtab Technology

This technology involves the preparation of rapidly disintegrating tablet, which consists of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, microencapsulation, extrusion-spheronization or simple pan coating method. The microcrystals or microgranules of the active ingredients are added to the granulated mixture of excipients prepared by wet or dry granulation and compressed into tablets.

14. Durasolv Technology

The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring low amounts of active ingredients.

15. Orasolv

The system essentially makes tablets that contain the taste masked active ingredients and an effervescent disintegrating agent, which on contact with saliva, rapidly disintegrates and releases the active ingredient. The tablets are made by direct compression at very low compression forces in order to minimize oral dissolution time. The tablets produced are soft and friable.

16 WOW tab

WOW means without water. This process uses a combination of low mouldability saccharide (rapid dissolution) and high mouldability saccharide (good binding property) to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide (lactose, mannitol) and granulated with a high mouldability saccharide (maltose, sorbitol) and compressed into tablets.

17. Dispersible Tablet Technology

It offers development of ODT with improved dissolution rate by incorporating 8-10% of organic acids and disintegranting agents. Disintegants include starch, modified starches, microcrystalline cellulose, alginic acid, cross-linked sodium carboxymethyl cellulose and cyclodextrins.

18. Pharma Burst Technology

It utilizes the co-processed excipients to develop ODT, which dissolves within 30-40s. This technology involves dry blending of dug, flavor, lubricant followed by compession into tablets.

19. Frosta Technology

It utilizes the concept of formulating plastic granules and compressing at low pressure to produce strong tablets with high porosity. The process involves usually mixing the porous plastic material with water penetration enhancer and followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15-30s depending on size of tablets.

20. Oraquick

It utilizes taste masking microspheres technology called as micromask, which provides superior mouth feel, significant mechanical strength, and quick disintegration/dissolution of

product. This form of matrix that protects drug, which can be compressed with sufficient mechanical strength. Oraquick product dissolves within few seconds.

21. Ziplets/Advatab

It utilizes water-insoluble ingredient combined with one or more effective disintegrants to produce ODT with improved mechanical strength and optimal disintegration time at low compression force.

22. Flash Dose technology

Flash dose technology has been patented by Fuisz. Nurofen meltlet, a new form of Ibuprofen as melt-in-mouth tablets. Flash dose tablets consist of self binding shearform matrix termed as"floss". Shearform matrices are prepared by flash heat processing.

MATERIALS AND EQUIPMENTS

Materials Used:

Sl. No.	Materials
1.	Domperidone
2.	Mannitol
3	Crospovidone
4.	Magnesium stearate
5.	Aspartame
6.	Aerosil
7	Flavor
8.	

Equipment Used:

Sl. No.	Equipment
1.	UV-spectrophotometer
2.	Digital Balance
3.	Digital pH meter
4.	Dissolution apparatus
5.	Hot air oven
6.	Hardness tester
7.	Friability test apparatus
8.	Tablet punching machine

METHODOLOGY

Formulation of Oral Disintegrating Tablets

Direct compression method

Oral disintegrating tablets of DOMPERIDONE were prepared by direct compression method according to the formulae given in the Table. All the ingredients were powdered separately, of which aerosil and magnesium stearate were passed through # 60 mesh sieve, and mannitol, crospovidone and aspartame were passed through # 30 mesh sieve. The drug and directly compressible excipients were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside. Then the other ingredients were mixed in geometrical order, in an inflated polyethylene pouch. Then these are punched with 6mm flat round punch to get tablets of 100 mg weight.

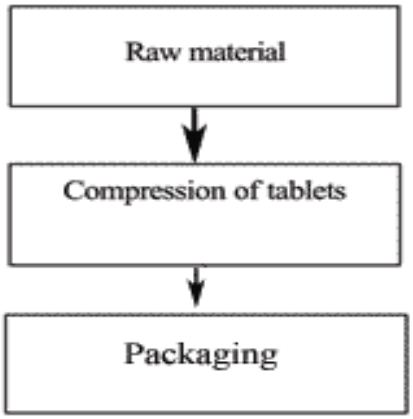

Fig 1: Direct compression method.

Table: Composition of DOMPERIDONE tablets prepared by direct compression (for 1 tablet).

S.no.	Ingredients	F_1 (mg)	F_2 (mg)	F_3 (mg)	F_4(mg)	F_5(mg)
1.	Domperidone	10	10	10	10	10
2.	Mannitol	82.8	81.8	80.8	79.8	78.8
3.	Crospovidone	1	2	3	4	5
4.	Magnesium stearate	0.6	0.6	0.6	0.6	5
5.	Aspartame	5	5	5	5	5
6.	Aerosil	0.6	0.6	0.6	0.6	0.6
7.	Flavour	q.s	q.s	q.s	q.s	q.s
8.	Total	100	100	100	100	100

Evaluation of Oral Disintegrating Tablets Of Domperidone

Pre compression parameters

The powder blend was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.

Bulk density (D_b): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It expressed in g/cc and is given by:

$$D_b = \frac{M}{V_0}$$

Where, M is the mass of powder, V_0 is the bulk volume of the powder.

Tapped density (D_t): It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2%). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by:

$$D_t = \frac{M}{V_1}$$

Where, M is the mass of powder, V_t is the tapped volume of the powder.

Carr's index (%): The bulk density is the measurement of weight to the volume of the sample. Tapped density is determined as the measurement of weight of the sample to the volume after tapping the measuring cylinder for 500 times from a height of 2 inches. The percentage compressibility (Carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to the tapped density.

$$\text{Carr's index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

Table: Flow property by Carr's index

Compressibility index (Carr's %)	Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Very very poor

Hausner's ratio: Hausner's ratio is the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better is the flow property. The powder with Hausner's ratio less than 1.18, 1.19-1.25, 1.3-1.5 and greater than 1.5 indicates excellent, good, passable and very poor flow properties, respectively.

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Angle of repose (θ): It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

$$\theta = \tan^{-1}(h/r)$$

Where, 'θ' is the angle of repose

'h' is the height in cms.

'r' is the radius in cms.

Table: Flow property by angle of repose

Angle of repose	Flow properties
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Post compression parameters

Weight variation: Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight. The results are shown in Table.

Table: Weight variation test.

Average weight of a tablet	% deviation
130mg or less	10
>130mg or <324mg	7.5
324mg or more	5

Hardness: Hardness was performed by Monsanto tester. Hardness was to be maintained within 2.0kg/cm^2 to 4.20 kg/cm^2, as these tablets are rapidly disintegrating. Three tablets are picked from each formulation; mean and standard deviation are noted. The results are shown in Table.

Friability: Friability of the tablets was checked by using Roche Friabilator. The device subjects a number of tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets from a height of 6 inches with each revolution. Pre-weighed sample tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. The results are shown in Table.

Fig: Monsanto tester

Fig: Roche friabilator

Content uniformity test: Ten tablets were weighed and powdered, a quantity of powder equivalent to 10 mg of domperidone was transferred to a 25 ml volumetric flask and 15 ml water is added. The drug domperidone is extracted in water by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and the liquid is filtered. The content was determined by measuring the absorbance at 285nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations. The results are shown in table.

Wetting time: This test is performed to know the tablet wetting time. A piece of tissue paper folded twice was placed in a small petridish (internal diameter 5 cm) containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured, the wetted tablet was then weighed.

Water absorption ratio: This test is performed to know the tablet wetting time. A piece of tissue paper folded twice was placed in a small petridish (internal diameter 5 cm) containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured, the wetted tablet was then weighed.

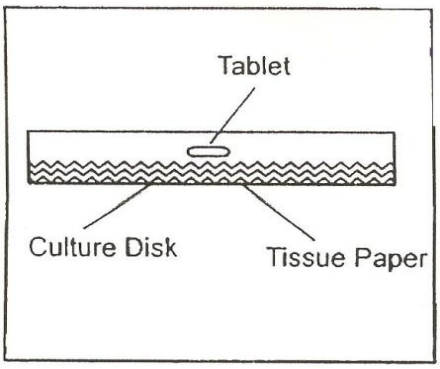

Fig.: Schematic representation of water absorption,

Water absorption ratio 'R' was determined using following equation

$$R = 100 \times \left(\frac{W_b - W_a}{W_a} \right)$$

Where, W_a is weight of tablet before water absorption and W_b is weight of tablet after water absorption.

Disintegration test: The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications.

I.P. specifications: place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using water maintained at 37^0+-2^0c. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded. Tablet was added to 100 ml of water at 37 ± 0.5° C. Time required for complete disintegration of a tablet was measured. The results are shown in table.

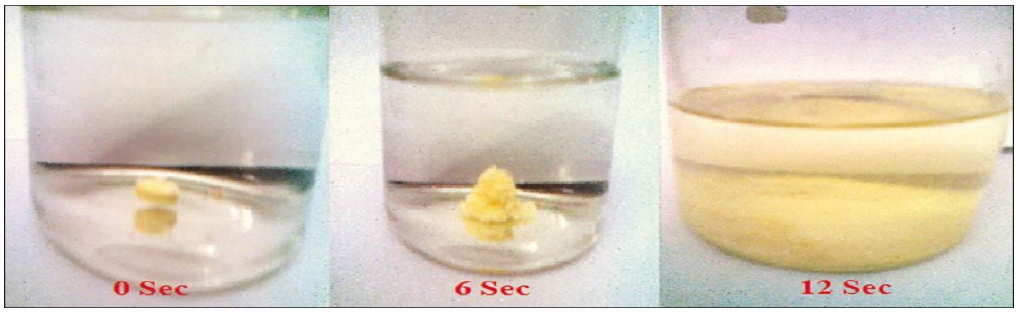

Fig: Disintegration process.

Dissolution study: In vitro dissolution of DOMPERIDONE mouth dissolving tablets was studied in USP XXIII type-II dissolution apparatus (Electrolab TDT-06N) employing a paddle stirrer at 50 rpm. 900 ml of pH 0.1N Hcl buffer was used as dissolution medium. The temperature of dissolution medium was maintained at 37 ± 0.5°C throughout the experiment. One tablet was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbances at 285nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent DOMPERIDONE released was calculated and plotted against time. For comparison the dissolution of DOMPERIDONE from commercial conventional tablet (CCF) formulation was also studied. The results are shown in table.

In vitro drug release study details

Apparatus used	:	USP XXIII type-II dissolution apparatus
Dissolution medium	:	0.1N Hcl buffer
Dissolution medium volume	:	900 ml
Temperature	:	37 ± 0.5^{o}C
Speed of paddle	:	50 rpm
Sample withdraw	:	5ml
Absorbance measured	:	285nm

Fig: Dissolution apparatus.

The results of in vitro release data obtained for all formulations were fitted in two popular models of data treatment as follows:

1. Zero-order kinetic model (Cumulative percent drug released versus time).
2. First order kinetic model (log cumulative percent drug remaining versus time).

Zero order kinetics

When the rate of drug release is independent or the amount of the drug remaining in the dosage form are constant over a period of time, it is said to be zero-order release. This is expressed mathematically as follows:

$$\frac{dC}{Dt} = K_r^0 \text{ ---------- (1)}$$

Where, C = Concentration of undisclosed drug

K_r^0 = Zero order release rate constant

t = time

Since "C" is constant, X the amount of drug release is identified as :

$$\frac{dC}{Dt} = K \text{ ---------- (2)}$$

Integration of the equation (2) yields:

$$X = Kt + \text{constant} \text{ ---------- (3)}$$

If the data from a release studies followed a zero order release, a plot of X versus, results in a straight line plot with slope equal to K, the value of K would indicate the amount of drug that is releasing per unit time and intercept of the line at time zero is equal to the constant in the equation (3).

First order release

When the rate of release is proportional to the first power of drug in the dosage form and expressed mathematically in the form of equation (4). Then the release is said to be first order with respect to drug in the dosage form.

$$\frac{dC}{C} = K_1\, dt \text{ ---------- (4)}$$

Where K_1 is the first order rate constant which on integration yields in natural logarithm form

$$\text{In } C = -K_1 t + \text{constant} \text{ ---------- (5)}$$

Or in common logarithm form

$$\log C = \left(\frac{K_1 t}{2.303}\right) + \text{constant} \text{ ---------- (6)}$$

Both equation (5) and (6) will be recognized as producing straight lines if In C or log C is plotted against t, this is an identifying characteristics of a release in which the rate of release is proportional to the concentration of the drug present in the dosage form.

RESULTS AND DISCUSSION

In the present study, an attempt has been made to formulate and evaluate mouth dissolving tablets of DOMPERIDONE by direct compression method, employing directly compressible excipients. Total five formulations were prepared. The composition of five formulations is given in Table. These tablets were evaluated for pre-compression parameters such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose and for post

compression parameters such as hardness, weight variation, drug content uniformity, wetting-time and water absorption ratio.

Preparation of standard calibration curve in 0.1N Hcl buffer

100mg of domperidone was dissolved in 100 ml of 0.1N Hcl. 5ml of this solution was taken and made up to 50ml with 0.1N Hcl. From the stock solution, concentrations of 2,4,6,8 and 10mcg/ml in water were prepared. The absorbances of these solutions were measured at 285 nm and standard plot was drawn using the data obtained. The correlation coefficient was calculated. The absorbance data of the above concentrations are shown in Table.

Table: Standard graph of DOMPERIDONE in 0.1N Hcl (λ_{max} 285nm).

Concentration(mcg/ml)	Absorbance
2	0.014
4	0.025
6	0.035
8	0.046
10	0.057

A = 0.005; B = 0.003; r = 0.999

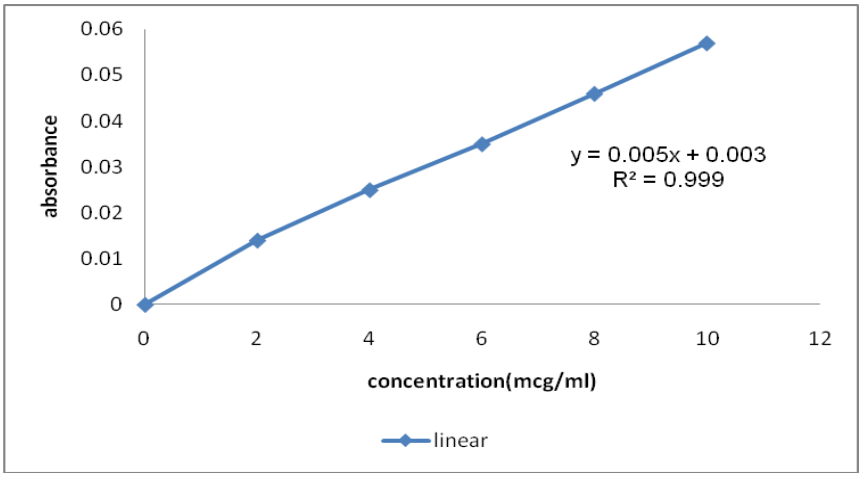

Fig: Standard graph of domperidone in 0.1N Hcl (λ_{max} 285nm).

Pre-compression parameters

Table: Pre-compression parameters of DOMPERIDONE formulations.

Formulation code	Bulk density (g/cc)	Tapped density(g/cc)	Angle of repose(degree)	Carr's index (%)	Hausner's ratio	Water absorption ratio
F_1	0.55	0.64	19.62	14.56	1.16	168+-1.92
F_2	0.52	0.55	19.24	15.45	1.057	174+-1.86
F_3	0.45	0.55	20.42	18.18	1.22	207+-1.93
F_4	0.53	0.62	19.24	16.120	1.99	209+-1.26
F_5	0.52	0.60	25.20	18.24	1.56	210+-1.46

The bulk density of pre-compression blends was found to be in the range of 0.45 to 0.55g/cc, tapped density in the range of 0.55 to 0.64gm/cc, the Carr's index values were in the range of 14.56 to 18.24%, Hausner's ratio in the range of 1.057 to 1.99 and angle of repose between 19.24 to 25.20.

The results are shown in table. The values obtained lies within the acceptable range. These results help in calculating the % compressibility. All the formulations showed good compressibility.

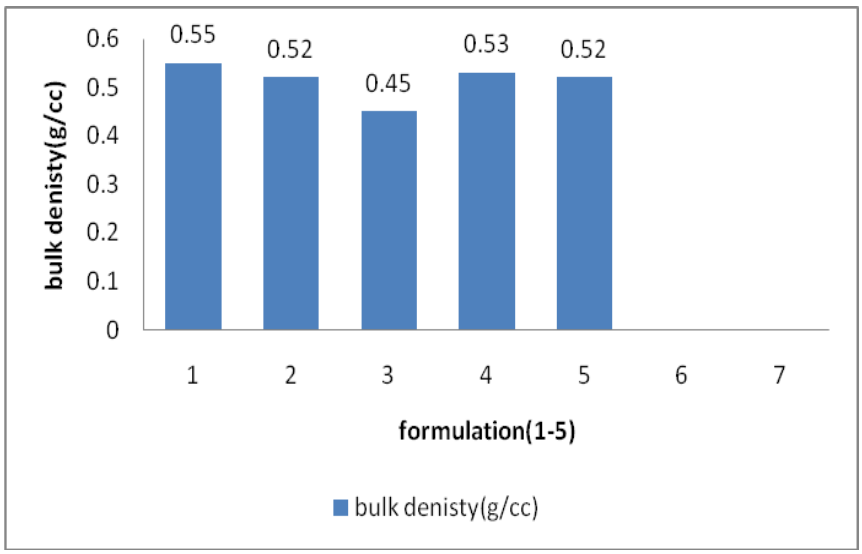

Fig: Comparison of Bulk density of domperidone powder (ODT) from formulation F_1 - F_5.

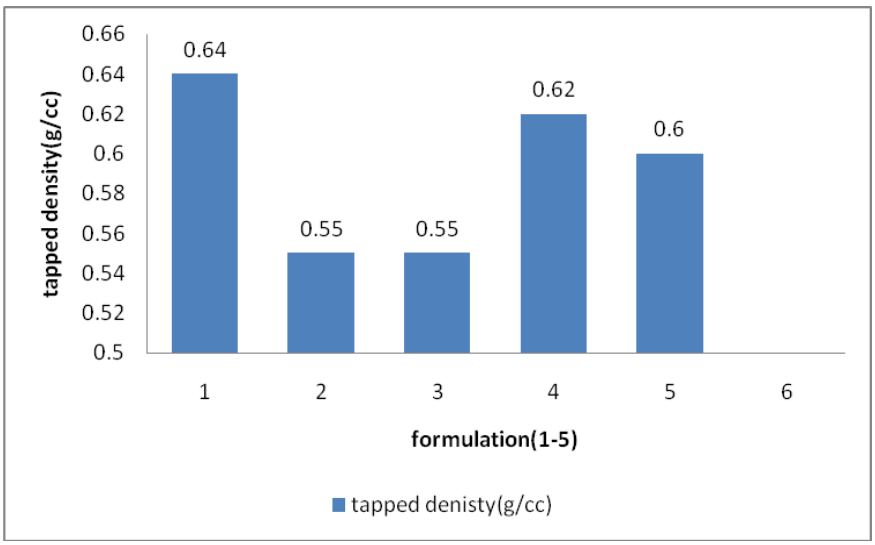

Fig: Comparison of tapped density of domperidone powder (ODT) from formulation F_1 - F_5.

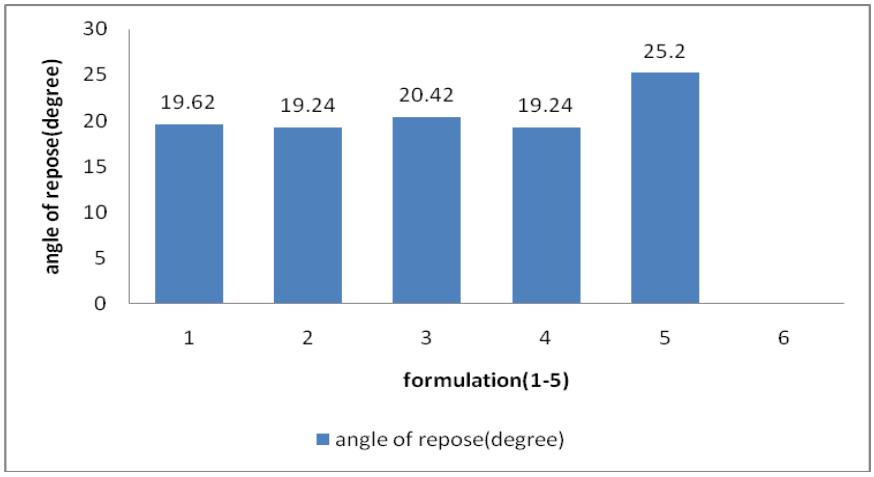

Fig.: Comparison of angle of repose of domperidone powder (ODT) from formulation F_1 - F_5.

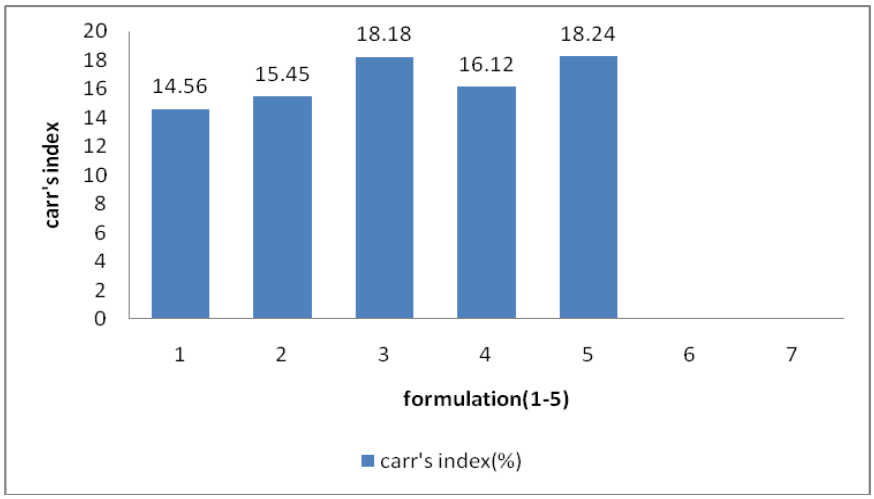

Fig.: Comparison of carr's index of domperidone powder (ODT) from formulation F_1 - F_5.

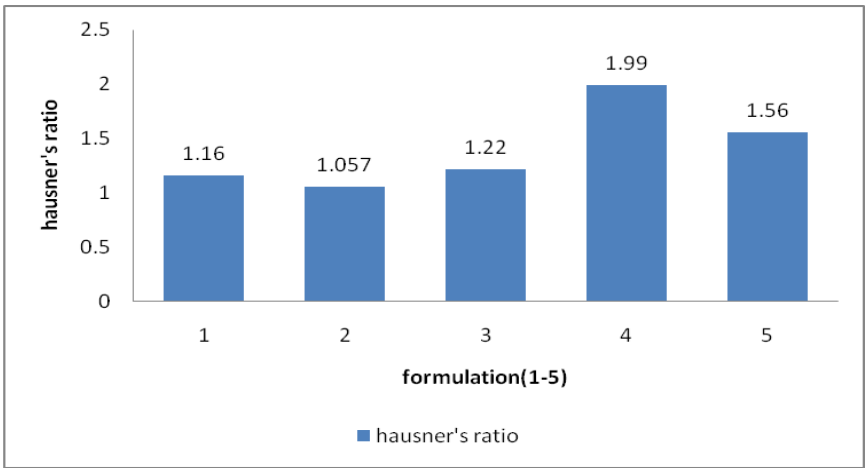

Fig: Comparison of hausner's ratio of domperidone powder (ODT) from formulation F_1 - F_5.

Post-compression parameters

Table: Post compression parameters of DOMPERIDONE tablets.

Formulation code	Hardness (kg/cm^2)	Friability (%)	Weight variation	Content uniformity (%)	Disintegration time(sec)	Modified disintegration test
F_1	2.3	0.11	Pass	99.98	26	24
F_2	2.0	0.12	Pass	99.90	22	18
F_3	3.1	0.11	Pass	99.36	18	11
F_4	2.5	0.10	Pass	99.94	12	9
F_5	3.0	0.11	Pass	99.96	11.9	8

Hardness and friability: The hardness of the tablet formulations made by both the methods was found to be in the range of 2.0 to 3.1kg/cm^2. The friability values were found to be in the range of 0.10 to 0.12%.

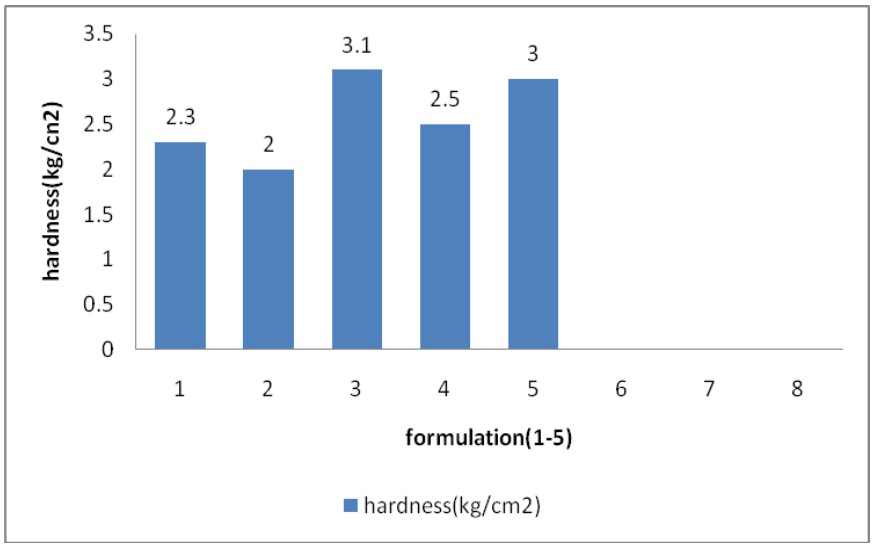

Fig.: Comparison of hardness of domperidone tablet (ODT) from formulation F_1 - F_5.

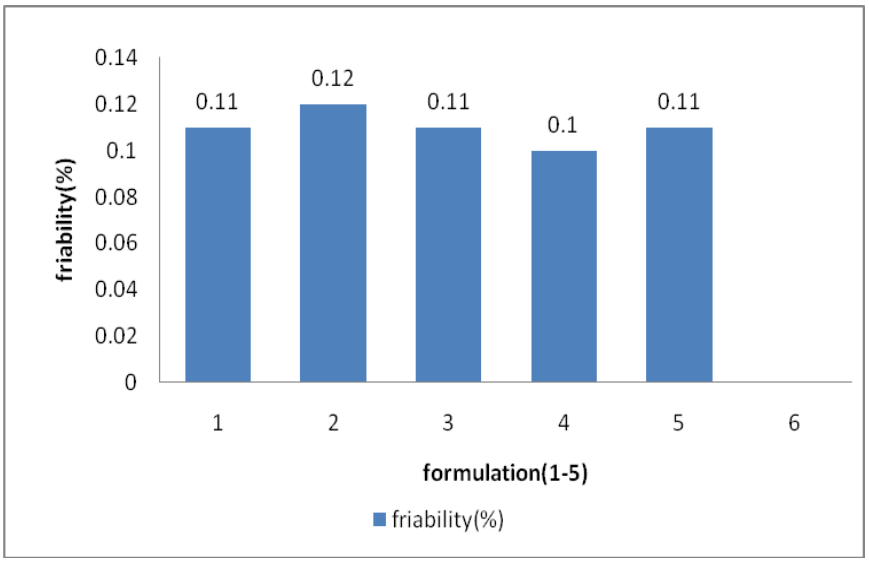

Fig: Comparison of %friability of domperidone tablet (ODT) from formulation F_1 - F_5.

Uniformity of weight: All the prepared mouth dissolving tablets of DOMPERIDONE were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits of ±7.5%.

Uniformity of drug content: The low values of standard deviation indicates uniform drug content within the tablets. The percent drug content of all the tablets was found to be in the range of 99.90 to 99.98% (which was within the acceptable limits of ±5%.

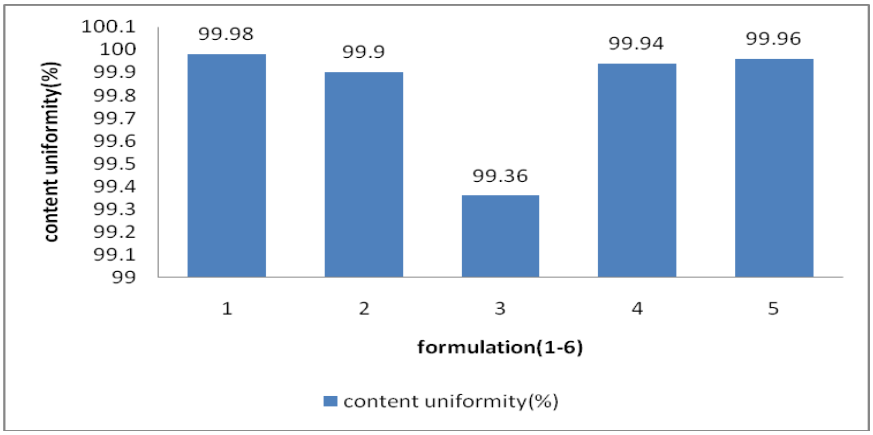

Fig.: Comparison of %content uniformity of domperidone tablet (ODT) from formulation F_1 - F_5.

In vitro disintegration time study

The internal structure of tablets, pore size distribution, water penetration into tablets and swelling of disintegration substance are suggested to be the mechanism of disintegration.

The results are shown in table. All the formulations showed disintegration time less than 30seconds.

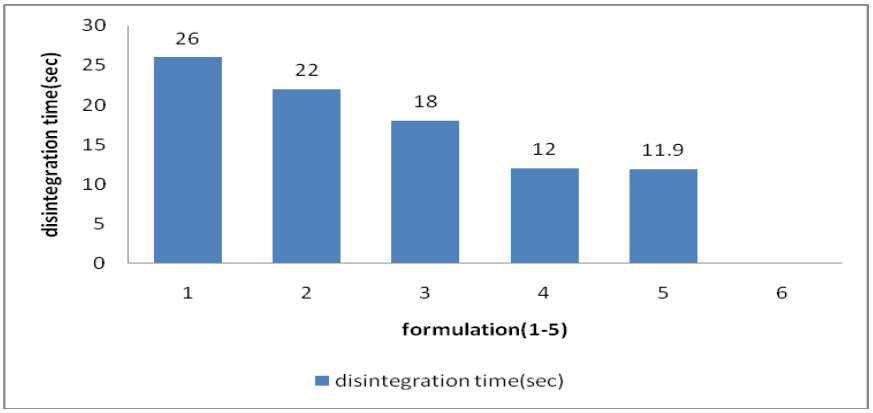

Fig.: Comparison of disintegration time of domperidone tablet (ODT) from formulation F_1 - F_5.

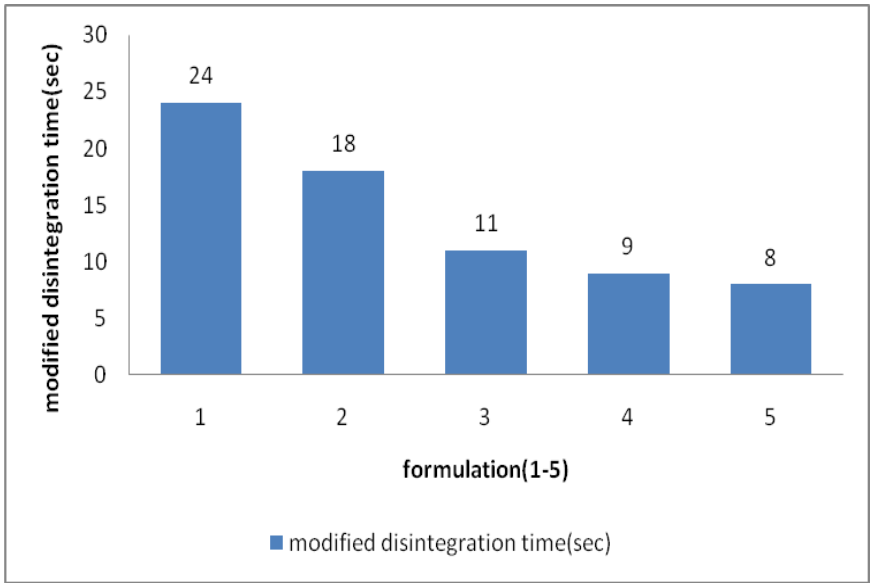

Fig.: Comparison of modified disintegration time of domperidone tablet (ODT) from formulation F_1 - F_5.

In vitro drug release studies

In vitro drug release profile of domperidone

Table : %cumulative amount of drug release of formulation F_1 - F_5.

S.no.	Time (min)	F_1(%)	F_2(%)	F_3(%)	F_4(%)	F_5(%)	Marketed Product(%)
1	5	52	56	65	79	82	67
2	10	65	67	78	92	95	79
3	15	78	79	89	99	102	91
4	30	86	90	100	103	104	101

Average of three determinations; Sd-Standard deviation

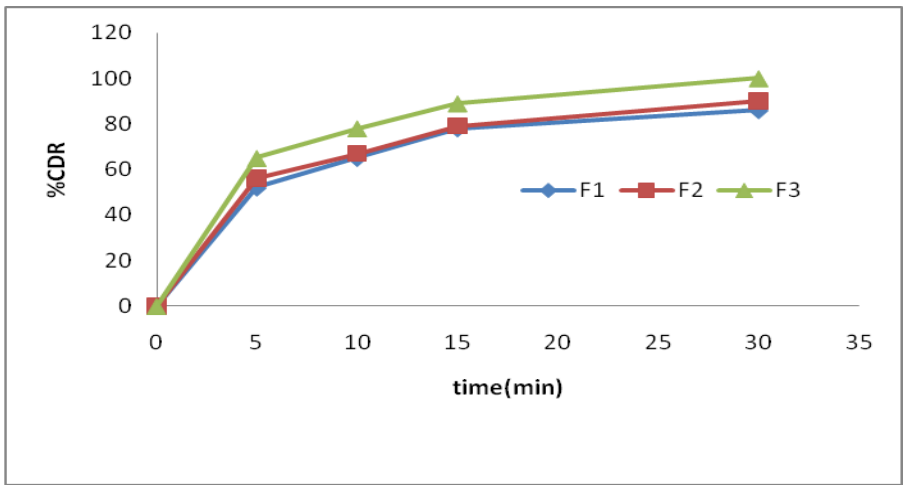

Fig.: In vitro drug release of domperidone (ODT) of formulation (F_1,F_2,F_3) in 0.1N Hcl.

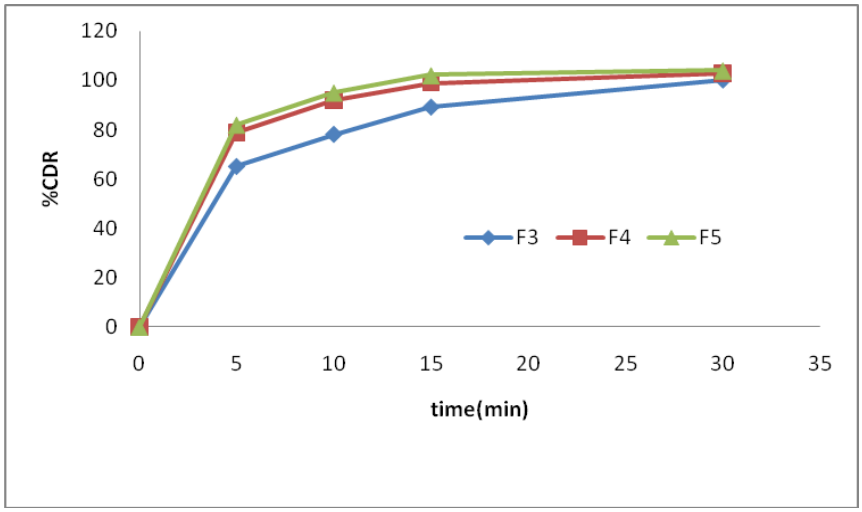

Fig.: In vitro drug release of domperidone (ODT) of formulation (F_3,F_4,F_5) in 0.1N Hcl.

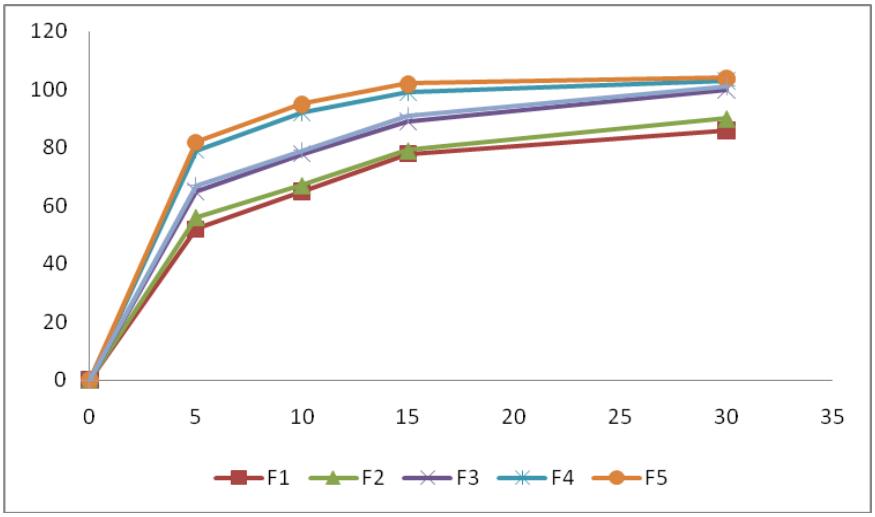

Fig: In vitro drug release of domperidone (ODT) of formulation (F_1 - F_5) in 0.1N Hcl.

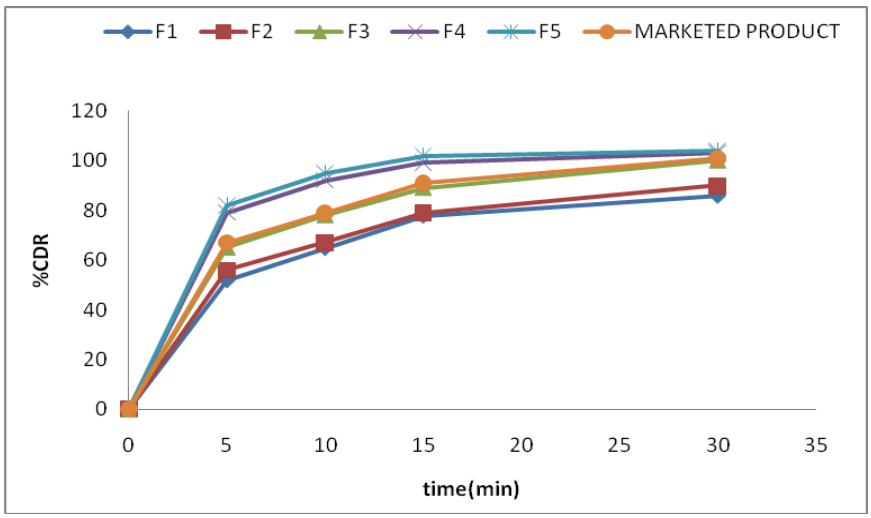

Fig: In vitro drug release of domperidone (ODT) of formulation (F_1 - F_5) and marketed in 0.1N Hcl.

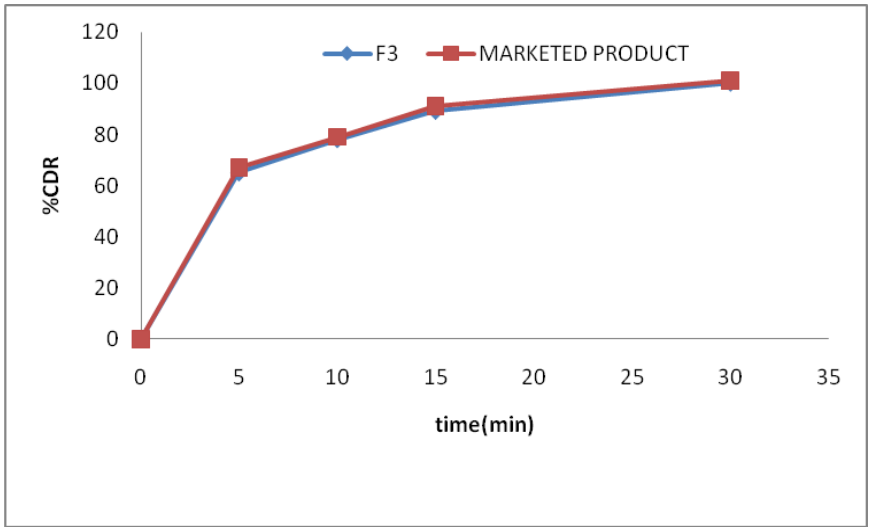

Fig: In vitro drug release of domperidone (ODT) of formulation (F_3) and marketed in 0.1N Hcl.

FORMULATION TRIALS

F_1 formulation has shown the good release profile from 5 to 10 minutes. But 100% release of the drug was not achieved within the specified time, that is, 30th minute. This can be minimized by increasing the concentration of disintegrating agent.

In F_2 formulation the concentration of the disintegranting agent is increased slightly. The percentage of drug released was increased when compared to the above formulation but failed to release completely within specified time, that is, 30th minute.

F_3 formulation has shown good release rate at 10th minute and prolonged the release upto 30th minute. This formulation has shown complete drug release at the end of dissolution profile time when compared to the above formulations.

In F_4 formulation the concentration of the disintegrating agent was again increased which resulted in the complete release of drug in 15 to 20 minutes. But this formulation was not recommended because it has shown its action before the specified time interval.

Further increase in the disintegrating agent in F_5 formulation, 100% drug is released by 15th minute. This was slightly faster than the marketed dissolution profile of ODT formulation.

Hence, F_3 formulation was considered as optimum formulation among the five formulations because it has shown 100% drug release by 30th minute.

SUMMARY AND CONCLUSION

Domperidone, an anti emetic drug used to speed the gastro intestinal peristalsis. The concept of formulating oral disintegrating tablets containing DOMPERIDONE offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increased bioavailability.

Recent advances in novel drug delivery (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for ease of administration and to achieve better patient compliance. One such approach is oral disintegrating tablets (ODTs). ODTs are solid unit dosage forms, which disintegrates or dissolves rapidly in the mouth without the general requirement for swallowing, the chewing and water. An oral disintegrating tablet provides an advantage particularly for pediatric and geriatric populations and who have difficulty in swallowing conventional tablets and capsules. This review depicts the various formulation aspects, technologies developed, ingredients used, evaluation tests and marketed formulations.

Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is oral disintegrating tablet formulation.

In the present work, oral disintegrating tablets of DOMPERIDONE were designed with a view to enhance patient compliance, by direct compression. In the direct compression method, crospovidone was used as disintegrant. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity, wetting time, water absorption ratio, In vitro dispersion time.

Among the tablets prepared by direct compression method formulation F_3 was found to be promising. This formulation was tested for in vitro drug release pattern (in 0.1N Hcl) which showed 100% drug release in 30 minutes and marketed product gave 101% in 30 minutes. The formulation F_3 has shown better control over drug release of marketed product

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