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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF DOMPERIDONE

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ABSTRACT

This work aims at investigating effect of concentration and type of polymer on formulation aspects of sustain release matrix tablets of anti-emetic containing 30 mg of a domperidone. The tablets were prepared by direct compression method because the flow property of drug was good. The Influence of concentration of polymer, type of polymer and mixture of polymers were studied with a view to optimize the formulation of domperidone. Prior to compression, different formulations were evaluated for flow and compression characteristics. All formulations were studied for *in vitro* drug release. The results showed that the optimum formulation (containing Carbopol 50% concentration) was able to retard the drug release up to 24 hrs. Release kinetics and mechanism of drug release from the formulation were also studied. The prepared tablets showed good mechanical properties. Tablets having Carbopol polymer showed good sustained release property and good reproducibility.

KEYWORDS: Domperidone, sustained release, direct compression, effect of concentration of polymer.

INTRODUCTION

In this model, drug in the outside layer exposed to the bathing solution isdissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows obviously that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions:

a) A pseudo-steady state is maintained during drug release.
b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.
c) The diffusion coefficient of drug in the matrix remains constant (no change occurs in the characteristics of the polymer matrix.
d) The bathing solution provides sink conditions at all times.
e) No interaction occurs between the drug and the matrix.
f) The total amount of drug present per unit volume in the matrix is substantially greater than the saturation solubility of the drug per unit volume in the matrix (excess solute is present).
g) Only the diffusion process occurs.

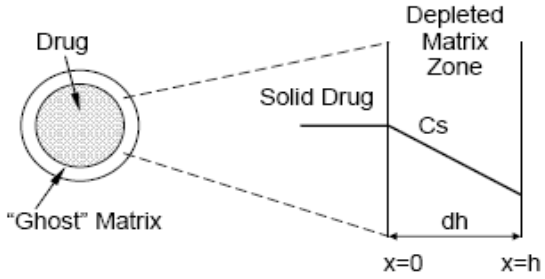

Figure 1: Schematic representation of a matrix system.

Bioerodible and combination diffusion and dissolution Systems 18

Strictly speaking, therapeutic systems will never be dependent on dissolution or diffusion only. In practice, the dominant mechanism for release will overshadow other processes enough to allow classification as either dissolution rate-limited or diffusion-controlled release.

As a further complication these systems can combine diffusion and dissolution of both the drug and the matrix material. Drugs not only can diffuse out of the dosage form, as with some previously described matrix systems, but also the matrix itself undergoes a dissolution process. The complexity of the system arises from the fact that as

the polymer dissolves the diffusional path length for the drug may change. This usually results in a moving boundary diffusion system. Zero-order release is possible only if surface erosion occurs and surface area does not change with time.

Swelling-controlled matrices exhibit a combination of both diffusion and dissolution mechanisms. Here the drug is dispersed in the polymer, but instead of an insoluble or non-erodible polymer, swelling of the polymer occurs. This allows for the entrance of water, which causes dissolution of the drug and diffusion out of the swollen matrix. In these systems the release rate is highly dependent on the polymer-swelling rate and drug solubility. This system usually minimizes burst effects, as rapid polymer swelling occurs before drug release.

With regards to swellable matrix systems, different models have been proposed to describe the diffusion, swelling and dissolution processes involved in the drug release mechanism. However the key element of the drug release mechanism is the forming of a gel layer around the matrix, capable of preventing matrix disintegration and further rapid water penetration.

When a matrix that contains a swellable glassy polymer comes in contact with a solvent or swelling agent, there is an abrupt change from the glassy to the rubbery state, which is associated with the swelling process. The individual polymer chains, originally in the unperturbed state absorb water so that their end to-end distance and radius of gyration expand to a new solvated state. This is due to the lowering of the transition temperature of the polymer (Tg), which is controlled by the characteristic concentration of the swelling agent and depends on both temperature and thermodynamic interactions of the polymer– water system. A sharp distinction between the glassy and rubbery regions is observed and the matrix increases in volume because of swelling. On a molecular basis, this phenomenon can activate a convective drug transport, thus increasing the reproducibility of the drug release. The result is an anomalous non-Fickian transport of the drug, owing to the polymer-chain relaxation behind the swelling position. This, in turn, creates osmotic stresses and convective transport effects.

The gel strength is important in the matrix performance and is controlled by the concentration, viscosity and chemical structure of the rubbery polymer. This restricts the suitability of the hydrophilic polymers for preparation of swellable matrices. Polymers such as carboxymethyl cellulose, hydroxypropyl cellulose or tragacanth gum, do not form the gel layer quickly. Consequently, they are not recommended as excipients to be used alone in swellable matrices.

The swelling behavior of heterogeneous swellable matrices is described by front positions, where 'front' indicates the position in the matrix where the physical conditions sharply change. Three fronts are present, as shown in Figure 2.

- The 'swelling front' clearly separates the rubbery region (with enough water to lower the Tg below the experimental temperature) from the glassy region (where the polymer exhibits a Tg that is above the experimental temperature).
- The 'erosion front', separates the matrix from the solvent. The gel-layer thickness as a function of time is determined by the relative position of the swelling and erosion moving fronts.
- The 'diffusion front' located between the swelling and erosion fronts, and constituting the boundary that separates solid from dissolved drug, has been identified.

During drug release, the diffusion front position in the gel phase is dependent on drug solubility and loading. The diffusion front movement is also related to drug dissolution rate in the gel.

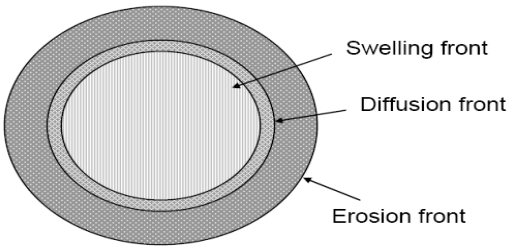

Figure 2: The fronts in a swellable HPMC matrix.

Drug release is controlled by the interaction between water, polymer and drug. The delivery kinetics depends on the drug gradient in the gel layer. Therefore, drug concentration and thickness of the gel layer governs the drug flux. Drug concentration in the gel depends on drug loading and solubility. Gel-layer thickness depends on the relative contributions of solvent penetration, chain disentanglement and mass (polymer and drug) transfer in the solvent. Initially solvent penetration is more rapid than chain disentanglement, and a rapid buildup of gel-layer thickness occurs. However, when the solvent penetrates slowly, owing to an increase in the diffusional distance, little change in gel thickness is observed since penetration and disentanglement rates are similar. Thus gel-layer thickness dynamics in swellable matrix tablets exhibit three distinct patterns. The thickness increases when solvent penetration is the fastest mechanism, and it remains constant when the disentanglement and water penetration occur at a similar rate. Finally, the gel-layer thickness decreases when the entire polymer has undergone the glassy–rubbery transition. In conclusion, the central element of the release mechanism is a gel-layer forming around the matrix in response to water penetration. Phenomena that govern gel-layer formation, and consequently drug-release rate, are water penetration, polymer swelling, drug dissolution and diffusion, and matrix erosion. Drug release is controlled

by drug diffusion through the gel layer, which can dissolve and/or erode.

MATERIAL AND METHODS

MATERIALS

Carbopol Himedim Laboratories, Mumbai, HPMC E15 Sd fine Chem Laboratories, Mumbai, Domperidone Yarrow Chemicals Pvt Ltd. Magnesium Stearate Himedim Laboratories, Mumbai, Talc Sd fine Chem Laboratories, Mumbai, Methanol Sd fine Chem Laboratories, Mumbai, Potassium Dihydrogen Phosphate Himedim Laboratories, Mumbai, Lactose monohydrate Sd fine Chem Laboratories, Mumbai.

METHODS

Analytical methods

Absorption maxima by UV spectrophotometer

Domperidone solutions were prepared in 0.1N HCl and phosphate buffer pH 6.8, solutions were scanned in the range of 200 to 400 nm using shimadzu UV spectrophotometer of model No.UV-2450, in order to determine the absorption maxima for analysis of dissolution samples.

Preparation of standard curve of Domperidone in 0.1N HCl

The concentrations of the drug (µg/ml) versus absorbance of drug at 284 nm was plotted to draw standard curve for estimation of drug dissolved during dissolution study. The concentration range of 5 to 25 µg/ml was selected for the preparation of standard curve in 0.1N HCl. The procedure for preparation of standard curve is given below.

Preparation of Domperidone stock solution in 0.1N HCl

10 mg of domperidone was dissolved in small quantity of methanolic HCl (2:3) in a volumetric flask and volume was made up to 50 ml to obtain a stock solution with concentration of 200 µg/ml.

Preparation of standard solutions

From the above stock solution, 0.25, 0.5, 0.75, 1, 1.25ml were withdrawn and diluted with 0.1N HCl in 10 ml volumetric flask to obtain a standard solution with concentration of 5, 10, 15, 20, 25µg/ml respectively .The absorbance of above standard solution was measured by using UV- visible Spectrometer model No: UV-2450 at a wavelength of 284 nm using 10 mm cuvettes. Then the standard graph of Concentration Vs Absorbance was plotted. Results were shown in Section 4.1.2.1 of Chapter 4.

Preparation of standard curve of domperidone in PH 6.8 phosphate buffer

The standard curve between the concentrations of the drug (µg/ml) Vs absorbance of drug at 284 nm was prepared for estimation of drug dissolved during dissolution study. The concentration ranges of 5 to 25 µg/ml were selected for the preparation of standard curve in phosphate buffer pH 6.8. The procedure for preparation of standard curve is given below.

Preparation of pH 6.8 phosphate buffer

Accurately weighed 68 gm of potassium dihydrogen phosphate and 9 g of sodium hydroxide pellets were dissolved in 10 L of water and adjust the pH with sodium hydroxide.

Preparation of domperidone stock solution in phosphate buffer pH 6.8

The accurately weighed 10 mg of domperidone was dissolved in small quantity of phosphate buffer pH 6.8 and volume was making up to 50 ml using a volumetric flask to obtain a stock solution with concentration of 200 µg/ml.

Preparation of standard solutions

From the above stock solution in pH 6.8 phosphate buffer, 0.25, 0.5, 0.75, 1, 1.25ml were withdrawn and diluted to 50 ml with pH 6.8 phosphate buffer using volumetric flask to obtained a standard solution with concentration of 5, 10, 15, 20, 25µg/ml respectively.

The absorbance of above standard solution was measured by using UV-Spectrometer model No: UV-2450 at a wavelength of 284 nm using 10 mm cuvettes. Then the standard graph of Concentration Vs Absorbance was plotted. Results were shown in Section 4.1.2.2 of Chapter 4.

Preformulation studies

Characterization of drug molecules is very important step at the Preformulation phase of product development. Following studies were conducted as basic Preformulation studies.

API characterization

Physical Characterization of domperidone

Organoleptic properties of Domperidone

The Organoleptic properties such as color and odor were evaluated.

Melting point

The melting point of the drug sample was determined by open capillaries using melting points apparatus.

Loss on drying (LOD)

Loss on drying was determined at 105°c using LOD apparatus.

Flow property of domperidone

The flow properties of the drug molecules are the important factor in selection of manufacturing process of formulation. The values of densities and the other parameters like Haunser's ratio and compressibility index, angle of repose were calculated. The scale of flowability is mentioned Table 3-7.

The bulk density and tapped density of the model drug was calculated to know the flow property of model drug and blends using the procedure given below.

Bulk density (B.D)

1. Around 15 g (M) of sample was weighed and transferred to a 50 ml measuring cylinder.
2. The volume (V_0) was noted.
3. B.D was calculated using the following formula;

$B.D = M / V_0$.

Tapped density (T.D)

1. The measuring cylinder of the previous test was mounted on the Tapped density apparatus (USP I).
2. Tapped 500 times and volume was noted as Va.
3. Tapped 750 times and volume was noted as Vb. (if the difference between Va and Vb was more than 2% then tapped for 1250 times).
4. The final volume was noted as Vf.
5. T.D was calculated using the following formula;

   T.D = M / Vf.

Hausner's ratio (H.R)

Hausner's ratio was calculated using the following formula.

H.R = T.D / B.D.

Compressibility index (C.I)

Compressibility index was calculated using the following formula.

C.I = 100 X (1 – 1/H.R.).

Table 3-4: Scale of flowability.

Compressibility Index	Angle of repose (degrees)	Hausner's Ratio	Flow Character
<10	25 – 30	1.00-1.11	Excellent
11-15	31 – 35	1.12-1.18	Good
16-20	36 – 40	1.19-1.25	Fair
21-25	41 – 45	1.26-1.34	Passable
26-31	46 – 55	1.35-1.45	Poor
32-37	56 – 65	1.46-1.56	Very poor

Angle of repose

The angle of repose of API and blends were determined by the funnel method. Accurately weighed quantities of samples were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the samples taken. The samples were allowed to flow through the funnel freely onto the surface. The height and diameter of the samples cone were measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

where h and r are the height and radius of the samples cone, respectively.

API-Excipients compatibility studies

In order to study the excipients compatibility of various excipients with domperidone, the mixture of domperidone with polymer was prepared and kept at 40±2º C/ 75±5% RH for 1 month.

FTIR Studies

FTIR spectra were routinely analyzed for drug excipients interactions. Pure Domperidone, HPMC E15, Carbopol, Domperidone and HPMC E15 (1:5), Domperidone and HPMC E15 (1:7), Domperidone and Carbopol (1:5), Domperidone and Carbopol (1:7) samples were analysed for any interaction between drug and polymer.

Formulation Development

The studies were planned with composition as shown in Table 3-8 to study the followings parameters.

- The effect of polymer concentration.
- The effect of type of polymers.
- The effects of combination of polymers and concentration of two polymers.

Preparation of tablets

The direct compression technique was selected for the process of preparation of tablets of model drug as the drug exhibits good flow and compressibility. Talc and Magnesium Stearate were used as lubricant in varying concentration. Domperidone and diluent/polymer (Lactose/HPMC E15 or Carbopol) were passed through #30mesh.

Table 3-5: Composition of formulations, mg.

Ingredients	Amount, mg/tablet					
	F1	F2	F3	F4	F5	F6
Domperidone	30	30	30	30	30	30
HPMC E15	62.5	87.5	125	174	-	-
Carbopol	62.5	87.5	-	-	125	175
Lactose	90	40	90	40	90	40
Mg Stearate	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	250	250	250	250	250	250

Characterization of blends

All the trial batch formulation blends were studied for flow properties in the same process as described under the flow properties of domperidone section 3.7.1.

Evaluation of tablets

The prepared tablets were evaluated for General appearance, thickness, hardness, weight variation, friability and uniformity of weight.

General appearance

The prepared tablets were evaluated visually for their appearance, texture and tablets defects.

Uniformity of weight (Weight variation test)

20 tablets were weighed individually and collectively. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percent deviation was calculated using the following formula**.**

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

The percentage difference in the weight variation should be within the permissible limits of 10% as per the limits mentioned as per Indian pharmacopoeia (I.P 2007) as shown in Table 3-6.

Table 3-6: Weight variation limits.

Average weight	Percent difference
130mg or less	10
More than 130mg but lessthan 324mg	7.5
More than 324mg	5

Thickness

Thickness of the tablets was calculated by the use of vernier calipers**.**

Hardness test

Hardness (diametral crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The hardness was tested using hardness tester. The average of the five determinations was determined and reported.

Friability test

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This In-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Roche friabilator was used to measure the friability of the tablets. It was rotated at a rate of 25 rpm.

Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotations (i.e. in 4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0%. The percent friability was determined using the following formula.

$$(W_1 - W_2)/W_1 \times 100$$

Where, W_1 = weight of the tablets before test, W_2 = weight of the tablets after test.

Assay

Twenty tablets of (F5) formulation were taken and powdered. The powder of 100 mg was accurately weighed and taken in a 100 ml volumetric flask, dissolved in methanol and the solutions were made up to volume and filtered. 10 ml of the filtered solution was transferred to a 100 ml volumetric flask and made up to volume to yield concentrations of drug in range of linearity and percentage drug content was 99.98.

Dissolution studies

The prepared tablets were evaluated for the dissolution studies in both acidic and alkaline media as given below in the Table 3-7.

Table 3-7: Dissolution condition.

S.No	Parameters	Acidic medium	Alkaline medium
1	Medium	0.1 HCl	pH 6.8phosphate buffer
2	Volume	900ml	900ml
3	Apparatus	USP II	USP II
4	RPM	100	100
5	Temperature	37±2ºC	37±2ºC
6	Time points (hrs)	1, 2	3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 23, 24

1) 900 ml of 0.1N HCl was taken in a dissolution vessel at given temperature and dissolution was carried out for 2 hours at 100 rpm. The dissolution was carried out for given time intervals where the samples were withdrawn at particular interval and analyzed by UV spectrometer at 284 nm.
2) 900ml of pH 6.8 phosphate buffer was transferred into the dissolution vessels. The dissolution was carried out for given time intervals where the samples were withdrawn at particular interval and analyzed by UV spectrometer at 284 nm.
3) Dissolution tests were carried out in two media 0.1 N HCl and pH 6.8 phosphate buffer. Optimum formulation should have the following properties; Drug release in stomach should be minimal (<10%) and should give release greater than 90% in basic pH of duodenum and intestine within 24hrs.

Release studies

The regression analysis of the experimental data was done using statistical function of the MS-Excel program. The fitting of equations is described below.

Zero order

This model represented an ideal release profile in order to achieve the prolonged action. This was applicable to dosage forms such as transdermal systems, coated forms, osmotic systems, as well as matrix tablets with low soluble drugs.

$$\% \text{ Released} = K.\text{Time}$$

First order

This model was applicable to study of hydrolysis kinetics and to study the release profiles of dosage forms, such as those containing water-soluble drugs in porous matrices.

$$\log (\text{fraction unreleased}) = (K/2.303).$$

Matrix (Higuchi matrix)
This model was applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug. When the initial dug loading was below the solubility limit, release was achieved simple diffusion through the polymer.

$$\% \text{ Released} = K (\text{time}^{1/2})$$

Higuchi's model predicted the square root of time dependence of the mass of the drug released and in inverse square root of time dependence of the drug release rate.

Peppas-Korsmeyer equation
This model was widely used, when the release mechanism was not well known or when more than one type of release phenomena could be involved. It was simple semi-empirical model and is known as power law. %Released = K (time*n) or log (%Released) = log (K) + n.log (Time).

The 'n' value could be used to characterize different release mechanisms as shown in Table 3-8.

Table 3-8: Different release mechanisms based on 'n' value.[23]

'n'	Mechanism
0.5	Fickian diffusion (Higuchi Matrix)
0.5<n<1	Anomalous transport
1	Case-II transport (Zero order release)
n>1	Super Case-II transport

Swelling controlled release systems were rather difficult to model due to complex macromolecular changes occurring in the polymer during release.

Hixson- Crowell equation
When the initial drug loading was above the solubility limit, the dissolution of the drug in the polymer and drug release became the dissolution rate limited.
(Fraction unreleased) $^{1/3}$ = 1-K.Time or 1-(fraction unreleased) $^{1/3}$ = K.Time.

RESULTS AND DISCUSSION

Analytical methods

UV spectrum of API

API solution of 20µg/ml concentration was prepared in 0.1 N HCl and in phosphate buffer pH 6.8 separately. The solutions were scanned between the wavelengths 200 – 400 nm. The λ_{max} was found to be 284 nm in 0.1 N HCl as shown in the Figure 4-1. In phosphate buffer pH 6.8, the λ_{max} was found to be 284.2 nm as shown in the Figure 4-2

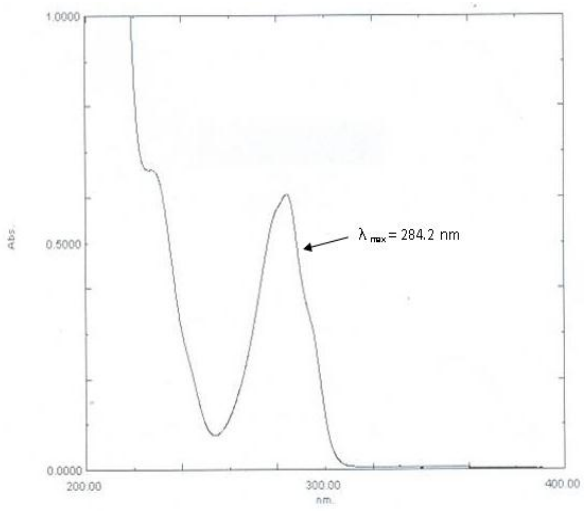

Figure 4-1: UV-Spectra of Domperidone (15 µg/ml) in 0.1N HCl.

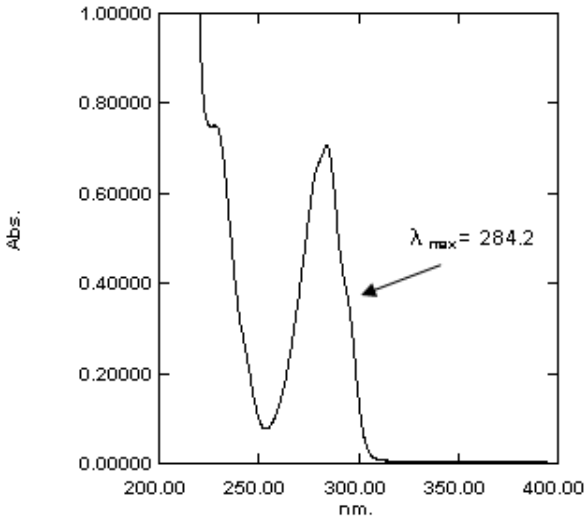

Figure 4-2: UV-Spectra of Domperidone (15 µg/ml) in 6.8pH phosphate buffer.

Standard curve of Domperidone
Standard curve of Domperidone in 0.1 N HCL
The values of absorbance of varying concentrations of model drug solution in 0.1N HCl at 284 nm are given in Table 4-1.

Table 4-1: Absorbance values of Domperidone in 0.1N HCl.

Concentration (µg/ml)	Mean absorbance ± S.D, (n=3)
5	0.21 ± 0.0053
10	0.441 ± 0.0081
15	0.643 ± 0.0089
20	0.871 ± 0.0082

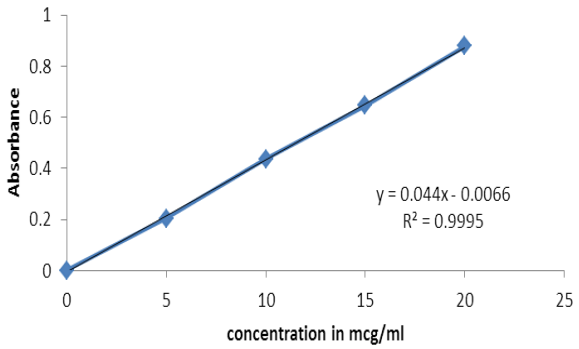

Figure 4-3: Standard curve of Domperidone in 0.1N HCl.

Linear relationship was observed between concentrations of drug solution (5-25 µg/ml) at 284 nm as shown in Figure 4-3. R^2 value was found to be 0.999, indicating that drug solution obeys Lambert-Beer's law in the concentration range of 5-25 µg/ml. Hence it was concluded that dissolution samples can be analyzed by measuring absorbance at 284 nm using UV spectrophotometer in the concentration range of 5-25 µg/ml.

Standard curve of Domperidone in phosphate buffer PH 6.8

The values of absorbance of varying concentration of domperidone solution in phosphate buffer pH 6.8 at 284.2 nm are given in Table 4-2.

Table 4-2: Absorbance values of Domperidone in phosphate buffer pH 6.8.

Concentration (µg/ml)	Mean absorbance ± S.D, (n=3)
5	0.238 ± 0.1555
10	0.476 ± 0.02050
15	0.716 ± 0.00565
20	0.966 ± 0.00282

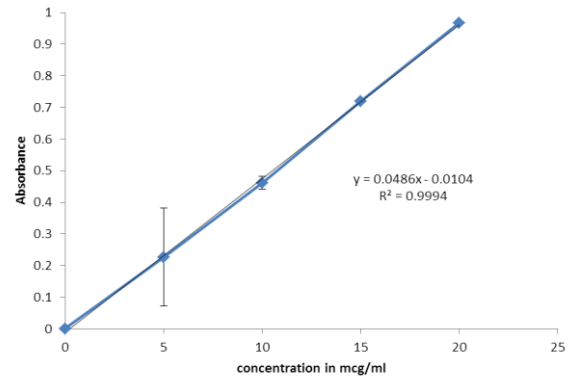

Figure 4-4: Standard curve of Domperidone in phosphate buffer pH 6.8.

Linear relationship was observed between concentration of drug solution (5-25µg/ml) and absorbance at 284 nm as shown in Figure 4-4. R^2 value was found to be 0.999, indicating that drug solution obeys Lambert-Beer's law in the concentration range of 5-25 µg/ml. Hence it was concluded that dissolution samples can be analyzed by measuring absorbance at 284.2 nm using UV spectrophotometer.

Preformulation studies

Domperidone characterization

Organoleptic properties of Domperidone

Color of the model domperidone was found to be white powder and odor less.

Physical and Chemical Characterization

Melting point

The procured sample of API was tested for its identification. The melting point of the Domperidone was found to be 242°C with reference to the literature it was found to be 240-245 °C.

Loss on drying, LOD

The loss on drying of the pure drug sample was determined at 105 °C and was found to be 0.26% w/w.

Flow properties

Flow properties of the model drug were represented in the Table 4-3.

Table 4-3: Flow properties of Domperidone.

Parameter	Value	Remark
Bulk Density (g/ml)	0.417	-
Tap Density(g/ml)	0.55	-
Compressibility Index (%)	31.894	Poor
Hausner's ratio	1.319	Passable
Angle of repose(degrees)	35.11	Good

The compressibility index and Hausner ratio indicated Passable of API and hence a suitable direct compression technology should be used for tablet manufacture.

Domperidone - Excipients compatability study

Binary mixtures of API and excipients were prepared in suitable ratios and evaluated for physical change as shown in Table 4-5 and FTIR study

Fourier transforms infra-red (FT-IR) spectroscopy analysis

FT-IR spectral studies were carried out for pure form and for the drug and polymer mixture. The IR spectra of Domperidone, HPMC E15, Carbopol, and their mixtures are shown in Figures 4.5-4.11 respectively.

The IR spectral analyses of domperidone are shown in Table 4.4.

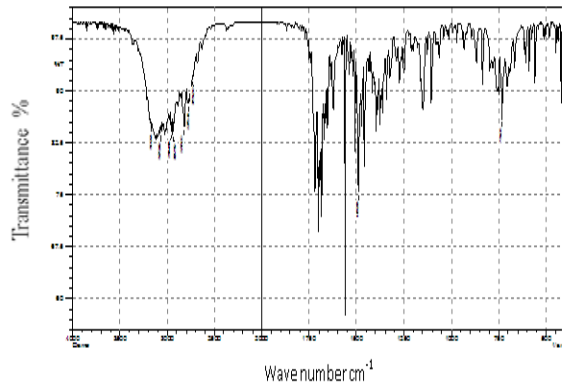

Figure 4.5: FT-IR spectrum of Domperidone.

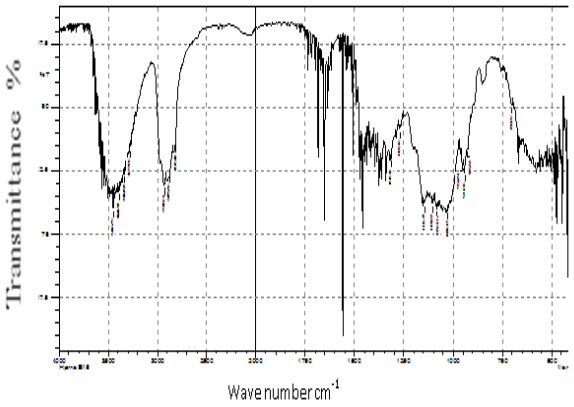

Figure 4.6: FT-IR spectrum of HPMC E15.

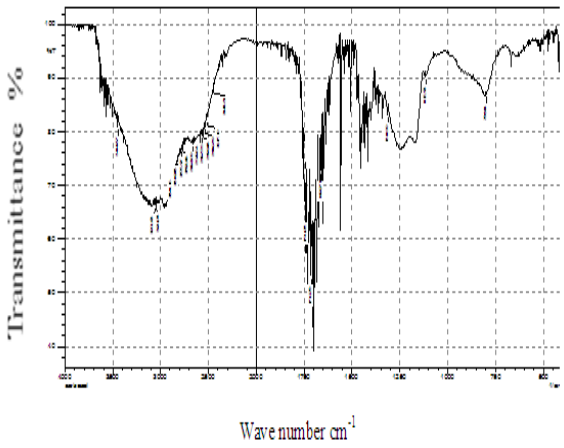

Figure 4.7: FT-IR spectrum of Carbopol.

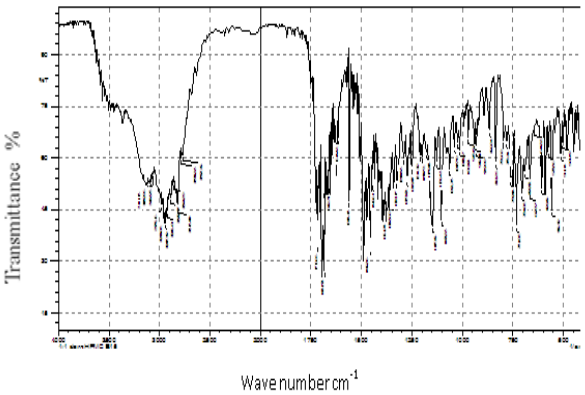

Figure 4.8: FT-IR spectrum of Domperidone and HPMC E15 in 1:5.

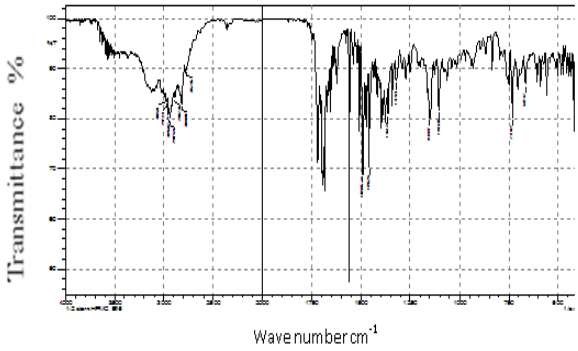

Figure 4.9: FT-IR spectrum of Domperidone and HPMC E15 in 1:7.

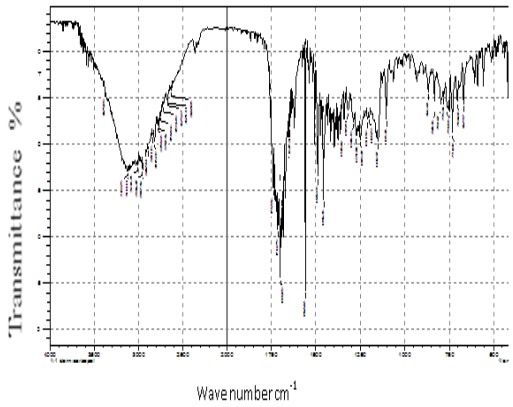

Figure 4.10: FT-IR spectrum of Domperidone and Carbopol in 1:5.

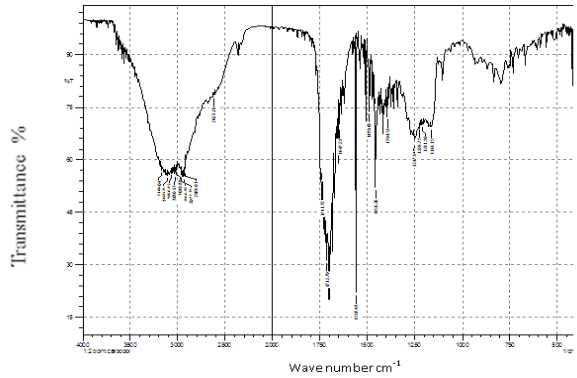

Figure 4.11: FT-IR spectrum of Domperidone and Carbopol in 1:7.

Table 4-4: FT-IR spectral analysis for Domperidone and Domperidone and polymer mixture.

Characteristic bands	Observed in study cm^{-1}	Literature values cm^{-1}
N–H stretching	3072.60	3100-3500
C=O stretch, sharp	1681.90	1640-1690
C-Cl bending, sharp	731.02	600-800

Table 4-5: Physical observations of Domperidone-Excipients compatibility study at 40°C/75%RH.

Binary mixture (Ratio)	Observations		
	Initial	After 15 Days	After 30 Days
Drug	off-white powder	off- white powder	off-white powder
Drug: Lactose anhydrous (1:3)	off-white powder	off-white powder	off-white powder
Drug: HPMC E15 (1:7)	off-white powder	off-white powder	off-white powder
Drug: Carbopol (1:7)	off-white powder	off-white powder	off-white powder

There were no changes in the physical appearance of drug excipients mixtures when stored at 40°C ± 2°C / 75% ± 5% RH for 1 month.

Formulation development

The main aim of the project is to formulate a sustained release matrix tablet of domperidone. With this goal, all the formulations were prepared and evaluated for % cumulative drug delivery in 0.1 N HCl and pH 6.8 phosphate buffer. The approach is to arrive at the optimum formulation.

In the present work HPMC E15 and Carbopol polymers were used to sustain the release of drug. Lactose anhydrous was used as diluent, talc as glidants, and magnesium stearate as lubricant. As the flow property of pure drug was passable and the dose of drug is 30 mg, the direct compression technique is selected in the present study. Hence wet granulation technology was not employed for the manufacture of tablets.

Modeling and Simulation

Statistical modeling will enable the scientists and engineers to clearly understand the quantitative relationship between the factors and response, i.e., quality characteristic. The impact of each factor and interaction effect on the quality characteristic can be best understood through the model further. The model will enable one to stimulate and find out the best parameters or formulation that satisfies the quality constraints.

Table 4-6: Absolute values of levels of variables.

S. NO	Variables	Levels	
		Lower level -1	Upper Level +1
1	HPMC E15	50	70
2	Carbopol	50	70

Preparation and Evaluation of Sustain Matrix Tablets

The oral sustain release matrix tablets were prepared by using different polymers at different concentrations and in different combinations by using direct compression method.

Preliminary Studies on Dummy Sustain Release Matrix Tablets

Preliminary studies were carried out to screen a set of concentration of polymers and type of polymer which shows feasibility to get a formulation which will sustain release of drug to 24 hours. As per the dosage form requirement, hydrophilic polymers were selected. The selected polymers were HPMC E15 and Carbopol to retard the Domperidone release from tablet. Lactose anhydrous was used as diluents. Magnesium stearate as Lubricant and Talc as glidant and the corresponding formulae are shown in Table 4.8. Dissolution studies performed on dummy tablets to find out the upper and lower concentrations of polymer that had shown a better retardation of drug from tablet.

Table 4-8: Formulations of dummy sustain release matrix tablets to find the effect of concentration of polymer.

Ingredients	Amount in mg/tablet					
	X1	X2	X3	X4	X5	X6
Domperidone	30	30	30	30	30	30
HPMC E15	125	150	175	-	-	-
Carbopol	-	-	-	125	150	175
Lactose	90	65	40	90	65	40
Mg Stearate	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	250	250	250	250	250	250

For the above six formulations dissolution studies were conducted. The drug release was sustained in X1, X2, X3, X4, X5, and X6 formulation.

Table 4-9: Cumulative % Drug release of X1, X2, X3 formulations having HPMC E15 (50%, 60%, 70% Concentrations respectively).

S. No.	Time in Hrs	X1	X2	X3
1	0	0	0	0
2	1	19.6	10.2	11.5
3	2	35.8	19.3	21.5
4	3	49.6	24.2	26.7
5	4	58.4	26.3	28.7
6	5	65.1	30.8	32.9
7	6	65.6	31.7	34.1
8	7	65.3	33.3	35.5
9	8	64.7	34	36
10	9	64.7	33.6	36
11	10	65.7	34.3	37.2

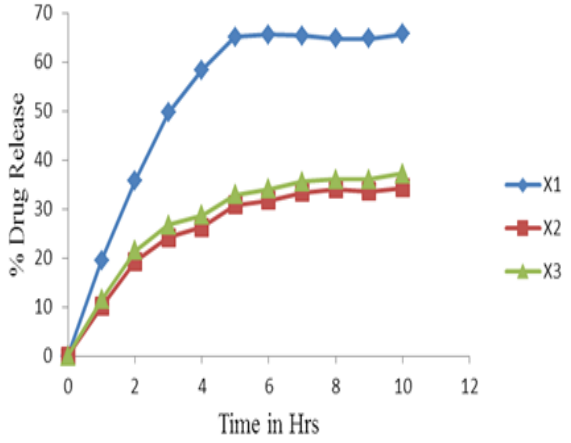

Figure 4-12: Cumulative % Drug release of X1, X2, X3 formulations having HPMC E15 (50%, 60%, 70% Concentrationsrespectively).

From the above dissolution studies, formulations X1 and X2 had shown 65.7% and 34.3 % drug release at the end of 10th hour respectively.

Table 4-10: Cumulative % Drug release of X4, X5, X6 formulations having Carbopol (50%, 60%, 70% Concentrations respectively).

S. No.	Time in Hrs	X4	X5	X6
1	0	0.00	0.00	0.00
2	1	7.64	7.54	15.38
3	2	11.87	13.33	21.12
4	3	13.39	14.66	23.11
5	4	14.71	15.14	25.74
6	5	18.49	17.85	31.73
7	6	19.46	20.18	44.66
8	7	23.27	26.39	56.30
9	8	25.22	29.60	67.17
10	9	27.39	34.09	72.13
11	10	29.88	38.07	76.07

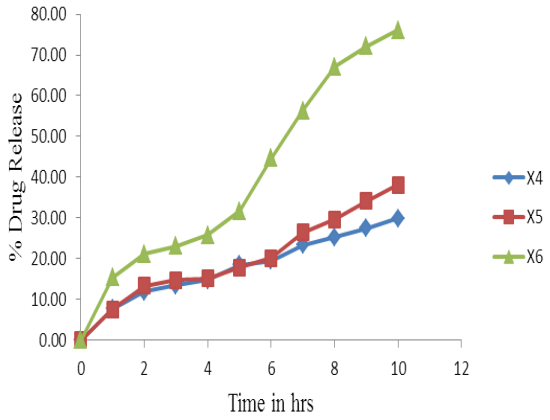

Figure 4-13: Cumulative % Drug release of X4, X5, X6 formulations having Carbopol (50%, 60%, 70% Concentrations respectively).

From the above dissolution studies, formulations X4 and X6 had shown 29.88 % and 76.07 % drug release at the end of 10th hour respectively.

From the above drug release pattern shown by different formulations it was concluded that concentrations of polymers were taken for optimization of formulation as 50% and 70% as lower limit and upper limit and the variables were polymer concentration, polymer type and their mixture.

As the sustain release matrix tablets are economical, was employed without application of enteric coating. To study the feasibility of preparation of matrix tablets, the following formula was used with the concentration of each component as represented in the Table 4- 11.

Study of effect of combination of Carbopol and HPMC E15

Dissolution studies were performed on optimized formulation to determine the best formulation that sustain the drug release for 24 hours.

Table 4-11: Composition of preliminary formulation F1, mg.

S.No.	Ingredients	Amount in mg per tablet
1	Domperidone	30
2	HPMC E15	62.5
3	Carbopol	62.5
4	Lactose anhydrous	90
5	Mg Stearate	2.5
6	Talc	2.5
7	Total weight	250

Study of pre-compression parameters of formulation blend of F1

Pre-compression parameters of formulation blend of F1 were studied to find the improvement in flow properties and presented in Table 4-12.

Table 4-12: Pre-compression parameters of formulation blend of F1.

Parameter	Result
Loss on Drying (%)	1.03
Bulk density (gm/cc)	0.60
Tapped density (gm/cc)	0.715
Compressibility index (%)	18.96
Hausner's ratio	1.190
Angle of repose (degrees)	28.56
Flow property	Good

Compressibility index, Hausner's ratio and angle of repose indicated the flow property of the formulation blend of F1 was good. In order to study the effect of ingredients on dissolution profile, the tablets were compressed by weighing the content of tablets individually and feeding to the compression machine. The prepared formulations were subjected to the further studies and the results are shown below.

Physical parameters of formulation F1 tablets

Physical parameters of formulation F1 tablets were studied and reported in Table 4-13.

Table 4-13: Physical parameters of F1 formulation tablets.

Parameters	Result (n=3)
Uniformity of weight (mg)	252 ± 1.40
Thickness (mm)	4.56 ±0.011
Hardness (Kp)	6.2 ±0.408
Friability (%)	0.2 ± 0.01

Dissolution studies

The acceptance criteria for drug release from the prepared sustained release formulation was set and cumulative drug release should not be more than 10% in acid stage and and not less than 90 % of the drug release in alkaline media in 24 hours. Batch F2 tablets were subjected to *in-vitro* dissolution studies in 0.1 N HCl and Phosphate buffer pH 6.8. The corresponding dissolution data was presented in the Table 4-14.

Table 4-14: Dissolution data of F1 formulation tablets in 0.1 N HCl.

S. No	Time (hrs)	Cum % drug release, mean ± sd (n=3) F1
1	0	0 ± 0.00
2	1	10.64 ± 2.21
3	2	15.48 ± 1.35
4	3	31.78 ± 3.01
5	4	42.21 ± 1.02
6	5	56.96 ± 3.3
7	6	65.58 ± 2.1
8	7	70.49 ± 1.32
9	8	75.63 ± 1.09
10	9	78.07 ± 2.31
11	10	83.57 ± 1.19
12	11	85.94 ± 2.15
13	12	92.72 ± 1.54
14	23	100.12 ± 1.62

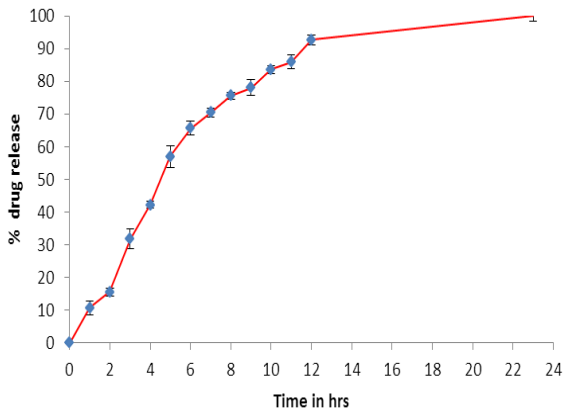

Figure 4-14: Dissolution profile of Formulation F1.

Study of effect of combination of Carbopol and HPMC E15

F2 formulation has been prepared and the composition was shown in the Table 4-15.

Table 4-15: Composition of formulation F2, mg.

S.No.	Ingredients	Amount in mg per tablet
1	Domperidone	30
2	HPMC E15	87.5
3	Carbopol	87.5
4	Lactose	40
5	Mg Stearate	2.5
6	Talc	2.5
7	Total weight	250

Pre-compression parameters of formulation blend – F2

Pre-compression parameters of formulation blend – F2 were done and the results were presented in the Table 4-16.

Table 4-16: Pre-compression parameters of formulation blend of F2.

Parameter	Result
Loss on Drying (%)	1.37
Bulk density (gm/cc)	0.589
Tapped density (gm/cc)	0.712
Compressibility index (%)	20.883
Hausner's ratio	1.209
Angle of repose (degrees)	29.21
Flow property	Fair

Compressibility index, Hausner's ratio and angle of repose indicate the flow property of the F2 formulation blend was fair.

Physical parameters of Formulation – F2 tablets

Physical parameters of F2 formulation tablets were represented in the Table 4-17.

Table 4-17: Physical parameters of F2 formulation tablets.

Parameters	Result (n=3)
Uniformity of weight (mg)	252.76 ± 1.42
Thickness (mm)	4.31 ± 0.15
Hardness (Kp)	5 ± 0.447
Friability (%)	0.06 ± 0.05

Dissolution studies

F2 batch tablets were subjected to *in-vitro* dissolution studies in 0.1 N HCl and pH 6.8 Phosphate buffer.

Table 4-18: Dissolution data of F2 formulation tablets.

S. No.	Time (hrs)	Cum % drug release, mean ± sd (n=3)
		F2
1	0	0 ± 0.00
2	1	8.63 ± 4.21
3	2	13.62 ± 2.32
4	3	29.92 ± 3.54
5	4	38.64 ± 1.65
6	5	45.81 ± 3.19
7	6	54.85 ± 2.62
8	7	59.95 ± 4.31
9	8	64.87 ± 4.22
10	9	67.25 ± 3.35
11	10	72.35 ± 2.12
12	11	75.52 ± 1.92
13	12	81.14 ± 1.85
14	23	100.54 ± 2.24

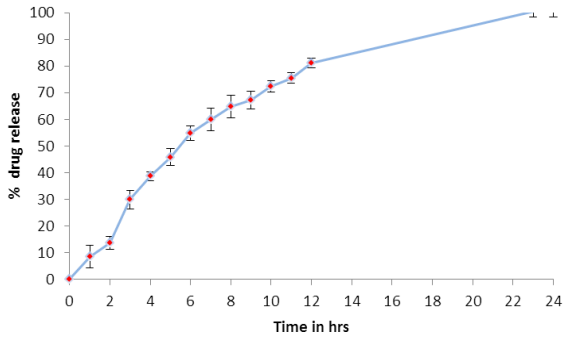

Figure 4-15: Dissolution profile of Formulation F2.

Study of effect of polymer concentration

F3 formulation has been prepared and the composition was shown in the Table 4-19.

Table 4-19: Composition of formulation F3, mg.

S.No.	Ingredients	Amount in mg per tablet
1	Domperidone	30
2	HPMC E15	125
3	Carbopol	-
4	Lactose	90
5	Mg Stearate	2.5
6	Talc	2.5
7	Total weight	250

Pre-compression parameters of formulation blend – F3

Pre-compression parameters of formulation blend – F3 were done and the results were presented in the Table 4-20.

Table 4-20: Pre-compression parameters of formulation blend of F3.

Parameter	Result
Loss on Drying (%)	1.4
Bulk density (gm/cc)	0.611
Tapped density (gm/cc)	0.736
Compressibility index (%)	20.458
Hausner's ratio	1.205
Angle of repose (degrees)	25.62
Flow property	Fair

Compressibility index, Hausner's ratio and angle of repose indicate the flow property of the F3 formulation blend was fair.

Physical parameters of Formulation – F3 tablets

Physical parameters of F3 formulation tablets were represented in the Table 4-21.

Table 4-21: Physical parameters of F3 formulation tablets.

Parameters	Result (n=3)
Uniformity of weight (mg)	252.12 ± 1.3
Thickness (mm)	4.37 ± 0.13
Hardness (Kp)	4.6 ± 0.258
Friability (%)	0.17 ± 0.09

Dissolution studies

F3 batch tablets were subjected to *in-vitro* dissolution studies in 0.1 N HCl and pH 6.8 Phosphate buffer.

Table 4-22: Dissolution data of F3 formulation tablets.

S. No.	Time (min)	Cum % drug release, mean ± sd (n=3)
		F3
1	0	0 ± 0.00
2	1	19.56 ± 3.2
3	2	35.79 ± 4.13
4	3	49.59 ± 2.45
5	4	58.39 ± 1.95
6	5	65.08 ± 2.63
7	6	66.95 ± 3.45
8	7	69.58 ± 4.11
9	8	72.65 ± 1.92
10	9	74.15 ± 1.99
11	10	76.36 ± 2.65
12	11	79.98 ± 4.55
13	12	85.78 ± 4.21
14	23	98.56 ± 3.96

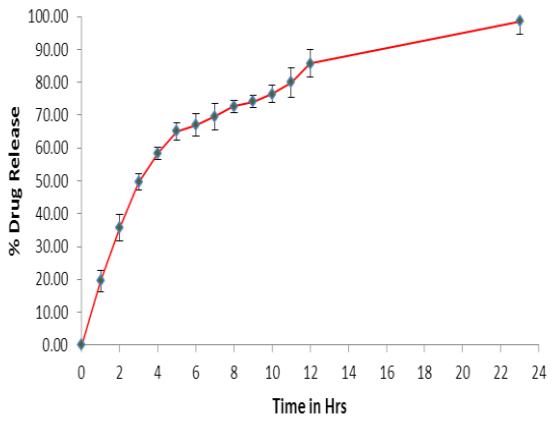

Figure 4-16: Dissolution profile of Formulation F3.

Study of effect of polymer concentration

F4 formulation has been prepared and the composition was shown in the Table 4-23.

Table 4-23: Composition of formulation F4, mg.

S.No.	Ingredients	Amount in mg per tablet
1	Domperidone	30
2	HPMC E15	175
3	Carbopol	-
4	Lactose	40
5	Mg Stearate	2.5
6	Talc	2.5
7	Total weight	250

Pre-compression parameters of formulation blend – F4

Pre-compression parameters of formulation blend – F4 were done and the results were presented in the Table 4-24.

Table 4-24: Pre-compression parameters of formulation blend of F4.

Parameter	Result
Loss on Drying (%)	1.2
Bulk density (gm/cc)	0.6122
Tapped density (gm/cc)	0.719
Compressibility index (%)	17.484
Hausner's ratio	1.175
Angle of repose (degrees)	28.36
Flow property	Good

Compressibility index, Hausner's ratio and angle of repose indicate the flow property of the F4 formulation blend was Good.

Physical parameters of Formulation – F4 tablets

Physical parameters of F4 formulation tablets were represented in the Table 4-25.

Table 4-25: Physical parameters of F4 formulation tablets.

Parameters	Result (n=3)
Uniformity of weight (mg)	251.79 ± 1.49
Thickness (mm)	4.49 ± 0.10
Hardness (Kp)	5.4 ± 0.37
Friability (%)	0.12 ± 0.07

Dissolution studies

F4 batch tablets were subjected to *in-vitro* dissolution studies in 0.1 N HCl and pH 6.8 Phosphate buffer.

Table 4-26: Dissolution data of F4 formulation tablets.

S. No.	Time (min)	Cum % drug release, mean ± sd (n=3)
		F4
1	0	0 ± 0.00
2	1	11.51 ± 2.1
3	2	21.51 ± 1.32
4	3	26.69 ± 4.32
5	4	28.68 ± 3.95
6	5	32.88 ± 1.63
7	6	34.10 ± 2.75
8	7	37.23 ± 2.35
9	8	39.35 ± 1.75
10	9	43.26 ± 1.99
11	10	45.36 ± 5.12
12	11	50.14 ± 3.51
13	12	59.71 ± 2.62
14	23	99.86 ± 3.16

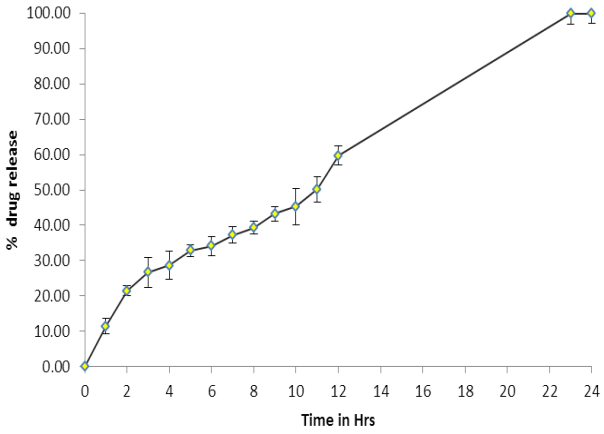

Figure 4-17: Dissolution profile of Formulation F4.

Study of effect of polymer concentration

F5 formulation has been prepared and the composition was shown in the Table 4-27.

Table 4-27: Composition of formulation F5, mg.

S.No.	Ingredients	Amount in mg per tablet
1	Domperidone	30
2	HPMC E15	-
3	Carbopol	125
4	Lactose	90
5	Mg Stearate	2.5
6	Talc	2.5
7	Total weight	250

Pre-compression parameters of formulation blend – F5

Pre-compression parameters of formulation blend – F5 were done and the results were presented in the Table 4-28.

Table 4-28: Pre-compression parameters of formulation blend of F5.

Parameter	Result
Loss on Drying (%)	1.37
Bulk density (gm/cc)	0.652
Tapped density (gm/cc)	0.752
Compressibility index (%)	15.337
Hausner's ratio	1.153
Angle of repose (degrees)	26.46
Flow property	Fair

Compressibility index, Hausner's ratio and angle of repose indicate the flow property of the F5 formulation blend was Fair.

Physical parameters of Formulation – F5 tablets

Physical parameters of F5 formulation tablets were represented in the Table 4-29.

Table 4-29: Physical parameters of F5 formulation tablets.

Parameters	Result (n=3)
Uniformity of weight (mg)	251.53 ± 1.45
Thickness (mm)	4.47 ± 0.12
Hardness (Kp)	6.8 ± 0.11
Friability (%)	0.08 ± 0.02

Dissolution studies

F5 batch tablets were subjected to *in-vitro* dissolution studies in 0.1 N HCl and pH 6.8 Phosphate buffer.

Table 4-30: Dissolution data of F5 formulation tablets.

S. No.	Time (hrs)	Cum % drug release, mean ± sd (n=3)
		F5
1	0	0 ± 0.00
2	1	7.53 ± 3.65
3	2	13.33 ± 2.11
4	3	14.66 ± 3.54
5	4	15.13 ± 1.75
6	5	17.84 ± 3.48
7	6	20.17 ± 2.86
8	7	26.38 ± 2.61
9	8	29.60 ± 3.73
10	9	34.08 ± 3.91
11	10	38.07 ± 1.97
12	11	42.69 ± 1.68
13	12	45.85 ± 4.35
14	23	99.94 ± 3.62
15	24	99.98 ± 2.33

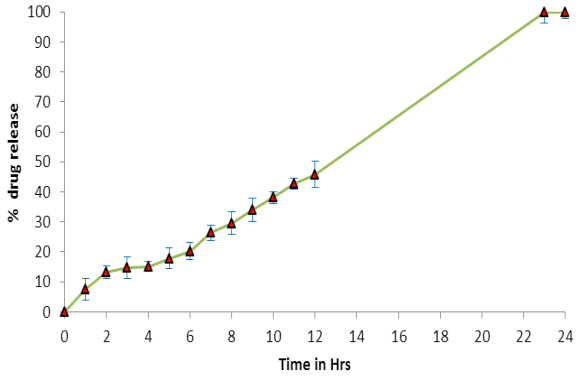

Figure 4-18: Dissolution profile of Formulation F5.

Study of effect of polymer concentration

F6 formulation has been prepared and the composition was shown in the Table 4-31.

Table 4-31: Composition of formulation F6, mg.

S.No.	Ingredients	Amount in mg per tablet
1	Domperidone	30
2	HPMC E15	-
3	Carbopol	175
4	Lactose	40
5	Mg Stearate	2.5
6	Talc	2.5
7	Total weight	250

Pre-compression parameters of formulation blend – F6

Pre-compression parameters of formulation blend – F6 were done and the results were presented in the Table 4-32.

Table 4-32: Pre-compression parameters of formulation blend of F6.

Parameter	Result
Loss on Drying (%)	1.37
Bulk density (gm/cc)	0.596
Tapped density (gm/cc)	0.701
Compressibility index (%)	17.617
Hausner's ratio	1.176
Angle of repose (degrees)	27.23
Flow property	Good

Compressibility index, Hausner's ratio and angle of repose indicate the flow property of the F6 formulation blend was Good.

Physical parameters of Formulation – F6 tablets

Physical parameters of F6 formulation tablets were represented in the Table 4-33.

Table 4-33: Physical parameters of F6 formulation tablets.

Parameters	Result (n=3)
Uniformity of weight (mg)	249.31 ± 1.32
Thickness (mm)	4.63 ± 0.14
Hardness (Kp)	6.4 ± 0.13
Friability (%)	0.15 ± 0.01

Dissolution studies

F6 batch tablets were subjected to *in-vitro* dissolution studies in 0.1 N HCl and pH 6.8 Phosphate buffer.

Table 4-34: Dissolution data of F6 formulation tablets.

S. No.	Time (hrs)	Cum % drug release, mean ± sd (n=3)
		F6
1	0	0 ± 0.00
2	1	15.38 ± 1.02
3	2	21.12 ± 2.12
4	3	23.10 ± 4.32
5	4	25.74 ± 4.02
6	5	31.72 ± 3.62
7	6	44.65 ± 2.95
8	7	56.29 ± 1.45
9	8	67.16 ± 2.95
10	9	72.13 ± 2.75
11	10	76.07 ± 3.62
12	11	82.65 ± 6.45
13	12	89.65 ± 4.26
14	23	99.81 ± 4.12
15	24	100.03 ± 1.26

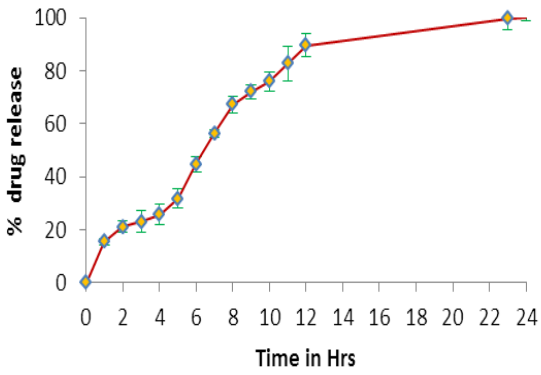

Figure 4-19: Dissolution profile of Formulation F6.

CONCLUSIONS

The objective of this study was to develop an optimum, stable, sustain release formulation of a high dose candidate drug to reduce frequency of dosage regimen. Domperidone selected for the study is an anti-emetic. The tablet parameters like weight variation, hardness, thickness, friability, disintegration time and dissolution were evaluated for all batches. Assay value of F6 formulation tablets was found to be 99.211% in phosphate buffer pH 6.8.The dissolution profiles of the prepared batches in 0.1 N HCl and phosphate buffer pH 6.8 studied. F5 formulation showed 99.98 % drug release at the end of 24 hour. Release kinetics studies of Formulation F5 showed Optimum formulation followed zero order drug release, and mechanism of drug release is diffusion.

The stability studies at 40°C and 75 % RH for 3 months showed the same drug release as that of initial sample of optimum formulation. From the above study it is concluded that a sustain release formulations can be prepared using Carbopol polymer which are cost effective, easy to manufacture and give reduced frequency of dosage regimen.

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