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Research Article

DESIGN, DEVELOPMENT AND EVALUATION OF DOMPERIDONE MALEATE BILAYER TABLETS

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ABSTRACT

Objective: Belayed tablets are preferred when the release profile of the drugs are different from one another (i.e.) in the present case 10 mg Domperidone Maleate has to be released Immediately and the remaining 20 mg of Domperidone Maleate has to be released in a sustained manner, so that therapeutic concentration can be maintained. Moreover Domperidone Maleate sustained release should be less in stomach and further release should be increased in the intestine and completed within twelve hours.The study was done to improve the patient compliance when the drug has been used in an extended release dosage form rather than conventional tablets. To perform the *in-vitro* dissolution profile of the formulated Belayed tablets. To reduce the incidence of adverse effects.

Method: The present work involves the formulation development, optimization and in-vitro evaluation of Belayed tablet containing Domperidone Maleate in the immediate release layer and in sustained release layer. Using Croscarmellose sodium as super disintegrant for the immediate release layer and the hydrophilic matrix formers such as HPMC K4M, HPMC K 100 M and Carbopol 974 NF for the sustained release layer.

Results: The present work involves the formulation development, optimization and in-vitro evaluation of Belayed tablet containing Domperidone Maleate in the immediate release layer and in sustained release layer. Using Croscarmellose sodium as super disintegrant for the immediate release layer and the hydrophilic matrix formers such as HPMC K4M, HPMC K 100 M and Carbopol 974 NF for the sustained release layer.

Belayed tablet showed as initial burst effect to provide dose of immediate release layer, followed by sustained release of Domperidone for 12 hours indicating a promising potential for the Belayed tablet of Domperidone Maleate sustained release and immediate release as an alternative to the conventional dosage form for the treatment of Vomiting and Nausea.

Conclusion: From the results formulation F -5 has been selected as best formulation among all the other formulations. Formulation F – 5 provides better in vitro release from layer 1 as well as layer 2. The data obtained from in vitro release study were fitted to various mathematical model like zero order, First order, Higuchi model and Peppas model. The results of mathematical model fitting of data obtained indicated that, the best fit model in all the cases the release was found to be by diffusion and nonfickian release.

Keywords: Bilayered tablets, Domperidone male ate, HPMC, sustained release layer and Carbopol.

INTRODUCTION[4,5]

Oral route of drug administration is the very important method of administering drugs for systemic effects. Nevertheless, it is probable that at least 90% of all drugs used to produce systemic effects are administered by the oral route.

Definition "Dual release tablet is a unit compressed tablet dosage form intended for oral application. It contains two layers in which one layer having conventional or immediate release part of single or multiple actives, another layer is sustained or controlled release part of single or multiple actives". They are also called as Belayed tablet, multi-layer matrix tablet.

Applications

- For combination therapy.
- To deliver the loading dose and sustained dose of the same or different drugs.
- To deliver the two different drugs having different release profiles.

Advantages

- They are used as an extension of conventional technology.
- Potential use of single entity of feed granules.
- Separation of incompatible components.
- Patient compliance is enhanced leading to improved drug regimen efficacy.
- Maintain physical and chemical stability.

Types of bilayer tablet press[9]

1. Single sided tablet press
2. Double sided tablet press
3. Belayed tablet press with displacement monitoring

1. Single sided press

Many types of bi-layer presses have been designed. Commonly used press is a single sided press which is having both chambers of the double feeder separated from each other. Each hopper is having gravity force fed with a different powder, thus producing the two individual layers of the tablet. When the die passes under the feeder, first loaded with the first layer powder it is followed by the second layer powder. The two layers in the die mix slightly at their interface in most cases bond sufficiently so that no layer separation occurs when the tablet is produced. This is the simplest way of producing a Belayed tablet.[11]

2. Double sided tablet press

Most double sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet or layer is measured by the control system at the main compression of the layer. This measured peak compression force is the signal used by the control system to reject out the tolerance tablets and correct the die fill depth when required.

3. Bilayer tablet press with displacement

The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre compression force.

MATERIALS AND METHODS

Materials

Domperidone Maleate(Jai Radhe Sales), Lactose Monohydrate, Microcrystalline Cellulose (Avicel - 102) and Croscarmellose

sodium(FMC Biopolymer), Povidone(K – 30) (ISP)Sunset Yellow, Quinoline Yellow(BASF), Isopropyl Alcohol(Merck),HPMC K4M, HPMC K 100 M (Dow Wolff Cellulosics)and Carbopol 974 NF(Lubrizol).

Methodology

A. Preformulation studies

A Preformulation activity ranges from supporting discovery's identification of new active agents to characterizing physical properties necessary for the design of a dosage form. Criticainformation provided during Preformulation can enhance the rapid and successful introduction of new therapeutic entities for humans.Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rationale development of dosage form.The overall objective of preformulation testing is to generate information useful in developing the formulation which is stable and bioavailable. Further the use of Preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product.For any drug substances to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug like physical appearance, solubility, bulk density, tapped density, compressibility, melting point, molecular weight.

B. Physical Appearance[20]

The appearance of the API was done by visual observation.

Bulk density

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring presieved blend into a graduated cylinder via a large funnel and measure the volume and weight as is given by

ρ_b =M/Vb

ρ_b = Bulk density

M = Mass of the powder

Vb = Bulk volume of the powder

Tapped Density

Tapped density is determined by placing a graduated cylinder containing known mass of blends on a mechanical tapped apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the tapped density may be computed.

Carr's Index/Compressibility Index

Carr's Index is measured by using the values of the bulk density and tapped density (Table 1).

CI= (TD-BD)/TD 100

Where, CI **=** Carr's Index/Compressibility Index

TD= Tapped Density, BD= Bulk Density

Hausner's Ratio

Hausner's ratio was determined as the ratio between the tapped density to that of the bulk density

Hausner's ratio **=** ρ_t / ρ_b

Where, ρ t= Tapped Density, ρ b= Bulk Density

Drug Excipients Compatibility Studies

The compatibility studies are carried out to study the possible interactions between Domperidone Maleate and inactive ingredients as well as Physical mixtures of both API and Excipients were prepared separately as per their ratios.

The pre-formulation study was carried out using drug and excipient compatibility studies. The results obtained from drug and excipient compatibility studies indicate that

the Domperidone Maleate is compatible with added excipients HPMC K 4M, HPMC K 100M, Carbopol 974 NF, Lactose Monohydrate, Microcrystalline Cellulose, Sunset Yellow lake, Quinoline Yellow lake and Magnesium Stearate. Thus further studies were carried out using these excipients.

Table 1: Composition of Domperidone Maleate IR Release Tablets Formulated by Wet Granulation Method.

Ingredients(mg/tablet)	IR 1	IR 2	IR 3
Domperidone Maleate	10	10	10
Lactose Monohydrate	85.85	64.85	55.85
Croscarmellose sodium	1	2	1
Sunset Yellow	0.15	0.15	0.15
Povidone	1	1	1
Purified Water	q.s	q.s	q.s
Microcrystalline Cellulose	-	20	30
Croscarmellose sodium	1	1	1
Magnesium Stearate	1	1	1
Total weight (mg)	**100**	**100**	**100**

Table 2: Composition of Domperidone Maleate Belayed Tablets Formulated by Wet Granulation Method.

Ingredients (mg)	SR 1	SR 2	SR 3	SR 4	SR 5	SR 6	SR 7	SR 8	SR 9
Domperidone Maleate	20	20	20	20	20	20	20	20	20
Lactose Monohydrate	80.28	-	-	117.78	77.01	-	-	70.28	105.7
Microcrystalline Cellulose	-	45.28	50.28	-	-	65.28	117.0	-	50
HPMC K 4 M	45	60	75	-	-	-	-	-	-
HPMC K 100 M	-	-	-	7.5	11.25	15.0	-	-	12.0
Carbopol 974 NF	-	-	-	-	-	-	11.25	15	4.58
Quinoline Yellow	0.22	0.22	0.22	0.22	0.22	0.22	0.22	0.22	0.22
Povidone K – 30	3	3	3	3	3	3	-	3	3
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	-	q.s	q.s
Microcrystalline Cellulose	-	20	-	-	37.02	45	-	40	-
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Weight of SR granules portion (mg)	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**
Weight of Belayed tablet (mg) (IR + SR Portion)	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Procedure

Manufacturing procedure

Granules were prepared using wet granulation method as per formulae given in **(Table 1&2)**. Domperidone bilayer tablets contained two layers i.e. an immediate release (IR) layer and a sustained release floating (SR) layer. All ingredients were passed through a sieve (30#) and mixed well in a mortar. Granules were prepared using purified water and povidone . Prepared granules dry with tray drier at temperature of 60^0C for 30 minutes. After the granules are dried, pass through a sieve (30#) a screen of smaller size than the one used for the wet mass select granules of uniform size to allow even fill in the die cavity. The selected granules lubricated with magnesium stearate. Weighed quantities of the SR layer equivalent to 150 mg were subjected to mild compression. Weighed granules of the immediate layer equivalent to 100 mg were added to the compressed SR layer. Both the layers were compressed into using 10/32 inch tablet shaped standard concave punch with 27 station double rotator rimek compression machine and where one cam was removed and air disgusting unit was fitted for sucking of excess powder to the overlap of powder. Firstly compression was done for IR part and compressed with SR part, keeping average weight 250 mg. After compression weight variation, friability, dissolution and assay test were carried out.

Table 3: Compression parameters for IR layer (final blend) tablets

Description	Light Orange colored round shaped tablets
Weight of individual tablet (mg)	100.0mg ± 3% (97.5 -102.9)
Weight of10 tablets (gm)	1.000gm ± 2% (0.800 – 1.200)
Hardness (kp)	2-3 kp
Thickness (mm)	2.45 mm

Table 4: Compression parameters for Domperidone Belayed tablets 30mg

Description	Slight Yellowish and Orange, Belayed, round shaped tablets
Weight of individual tablet (mg)	250.0mg ± 4% (246.0 – 254.0)
Weight of 10 tablets (gm)	2.500gm ± 3% (2.470 – 2.530)
Hardness(kp)	10 – 11 kp
Thickness(mm)	8.0m ± 0.5 (7.5 – 8.5)
Friability	Not more than 1.0% w/w

Evaluation[22]

a) Weight variation

The test ensures that all the tablets in each batch are of same potency, within limits. Each tablet in the batch should be uniform in weight and weight variation if any, should be generally within ± 10% for tablets weighing 130 mg or less, ± 7.5% for tablets weighing more than 130 mg and up to 324 mg and ± 5% for tablets weighing 325 mg or more. According to the official test, 20 tablets were weighed individually and collectively. Average weight per tablet was calculated from the collective weight. Then the weights of the individual tablets were compared with the average weight to determine weight variation.

b) Hardness test

Tablets require a certain amount of strength, or resistance to friability, to withstand the mechanical shocks of handling in manufacture, packaging, and shipping. The strength of the tablet was determined by LABINDIA tablet hardness tester. The force of fracture was recorded.

c) Friability

Friability test was performed to assess the effect of friction and shock which may often cause tablets to chip, cap or break. It generally reflects poor cohesion of tablet ingredients. Weighed tablets sample was placed in the chamber and the friabilator was operated for 100 revolutions at 25 RPM and the tablets were weighed again. Compressed tablets should not lose more than 1% of their weight.

d) Tablet thickness

Variation in the tablet thickness may cause problems in counting and packaging in addition to weight variation beyond the permissible limits. Tablet thickness should be controlled within a ± 3% of a standard value. Tablet thickness was measured by Vernier calipers.

e) Disintegration test

The first important step is break down of the tablet into smaller particles or granules, a process known as disintegration. The USP device used to test disintegration uses 6 glass tubes that are 3 inches long, open at the top, and held against a 10 mesh screen at the bottom end of the basket rack assembly. To test for disintegration time, six tablets were placed in the six tubes of the apparatus and the basket rack is positioned in a one liter beaker of water, simulated gastric fluid, or simulated intestinal fluid, at 37 ± 2^0C, such that the tablets remain 2.5 cm below the surface of the liquid on the upward movement and not closer than 2.5 cm from the bottom of the beaker. A standard motor device is used to move the basket assembly containing the tablets up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute. Perforated plastic discs may also be used in the test.

f) Drug content

Assay (By UV Spectrophotometer)

The Bilayer tablets were prepared and evaluated for assay. Each Bilayer tablet contains 10mg of Domperidone Maleate IR Portion and 20mg of Domperidone Maleate SR Portion.

Preparation of standard solution

Accurately weigh and transfer about 30mg of Domperidone Maleate working standards into a 100ml volumetric flask. Add about 25ml of methanol and sonicate to dissolve. Dilute to volume with Diluents and mix. Transfer 1.0ml of the above solution into a 50ml volumetric flask, dilute to volume with diluents and mix.

Preparation of sample solution

Transfer 5 tablets into a mortar and crushed into fine powder blend. Weigh 250mg equivalent sample from this and transfer into a 100 ml volumetric flask. Add about 25ml of methanol and sonicate to dissolve. Dilute to volume with Diluent and mix. Transfer 1.0ml of the above solution into a 50ml volumetric flask, dilute to volume with diluent and mix.

Procedure

Flush the UV Spectrophotometer cuvettes thoroughly with water followed by methanol. Stabilize the system for not less than 30minutes with blank solution (0.1 N HCl). Samples are typically placed in the cuvettes containing standard solution and blank as a reference in another cuvette, this is measured against the sample solution. The absorbance of both standard and sample solutions is noted and drug content is estimated.

$$\text{Assay} = \frac{\text{Absorbance of sample solution X 100}}{\text{Absorbance of standard solution}}$$

g) Dissolution study

Belayed tablets were prepared and evaluated for invitro drug release. Each Belayed tablet contains 10mg of Domperidone Maleate IR Portion and 20mg of Domperidone Maleate SR Portion.The in vitro dissolution study was was performed using LABINDIA DISSO 2000 an eight stage dissolution rate testing apparatus with basket. The study was carried out in using USP Type II dissolution apparatus containing 900ml. The dissolution fluid was 900ml 0.1 N HCl and Phospahte buffer pH 6.8 at a speed of 100rpm & a temperature of 37±0.5°C were used in each test. Samples of dissolution medium (5ml) were withdrawn through a filler of 0.45µm at different time intervals, suitably diluted and assayed for Domperidone by measuring absorbance at 284nm. These studies were conducted in triplicate.

RESULTS

Preformulation study

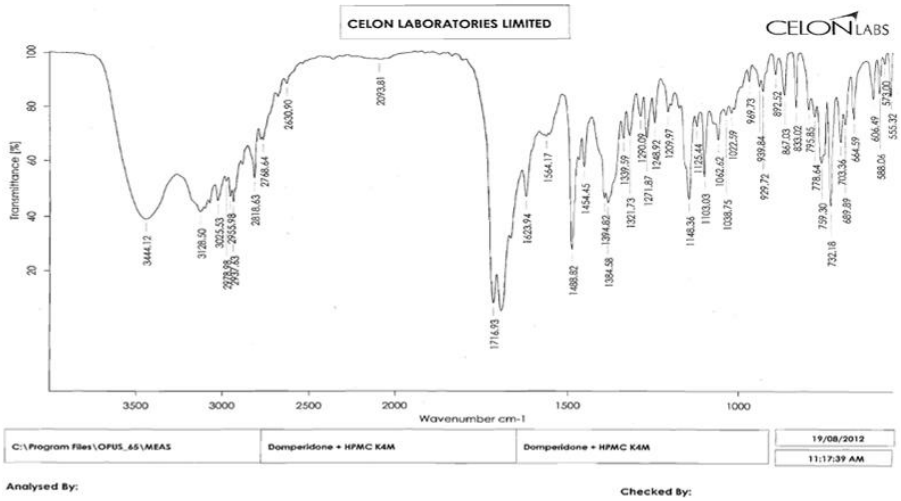


Fig. 1: FTIR spectrum of Pure Domperidone Maleate

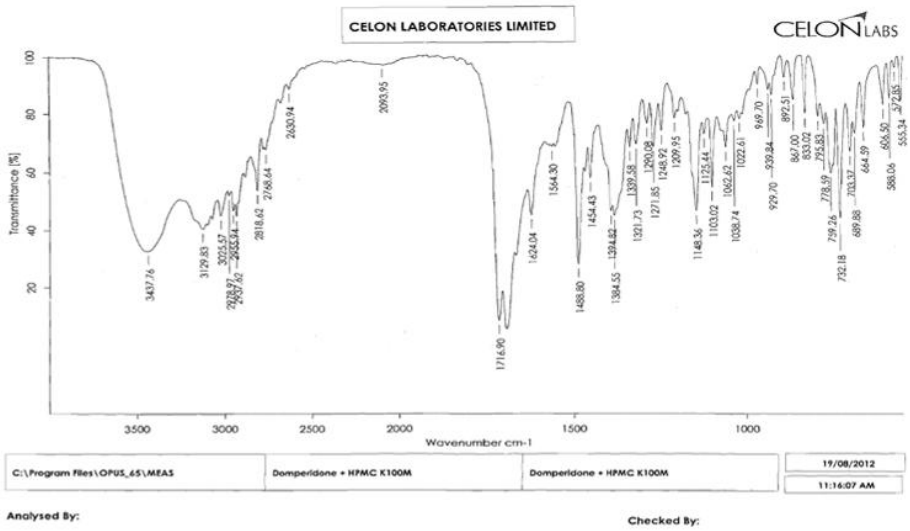


Fig. 2: FTIR spectrum of Domperidone Maleate + HPMC K 100M

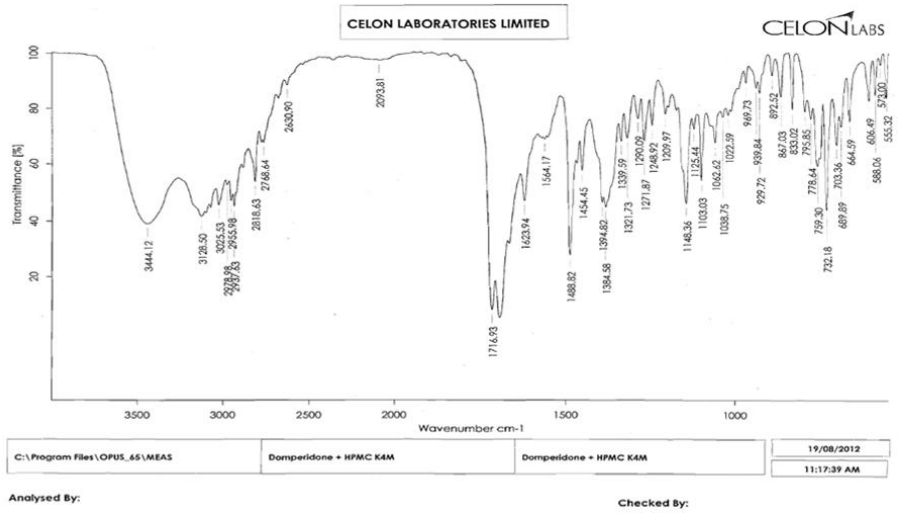


Fig. 3: FTIR spectrum of Domperidone Maleate + HPMC K 4M

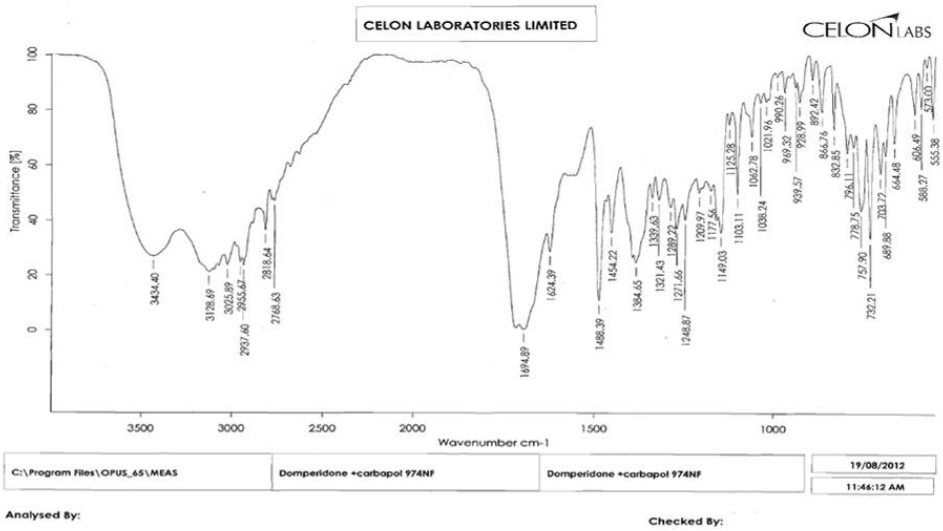


Fig. 4: FTIR spectrums of Domperidone Maleate + Carbopol 974 NF

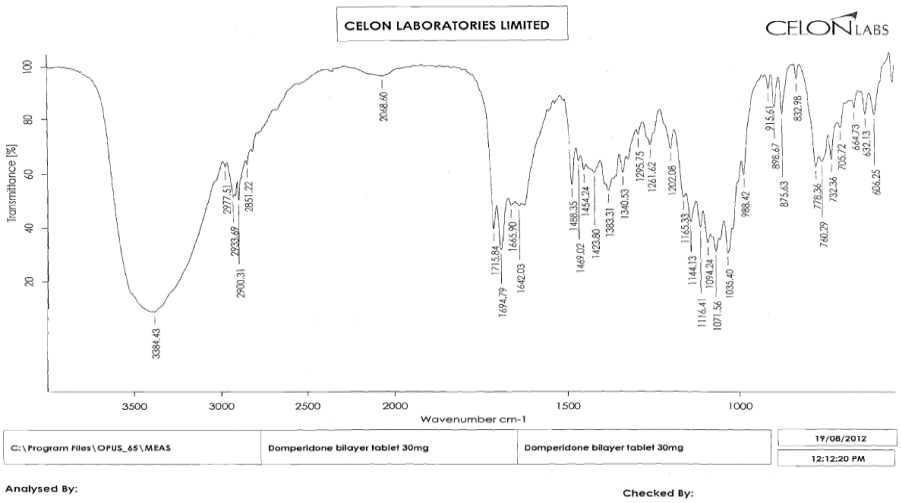


Fig. 5: FTIR spectrum of Domperidone Maleate Belayed Tablet

Drug content

The Drug content of the Bilayer Domperidone Tablet was estimated and found to be:

$$\text{ASSAY} = \frac{\text{Absorbance of sample solution X 100}}{\text{Absorbance of standard solution}}$$

$$= \frac{0.858 \text{ X } 100}{0.855}$$

= 100.53 %

Micromeritic properties

- Hausner's ratio and percentage compressibility of SR-8 Were found to be 1.04 and 9.96 respectively, which indicates poor flow.
- In SR-5, the fluid uptake was increased, to improve flow property of SR layer. Hausner's ratio, angle of repose and percentage compressibility of SR-5 Were found to be 1.11, 31.84^0 and 10.05 respectively, which indicates good flow.
- Remaining all batches from SR-3 to SR-8 Showed good flow based on the compressibility and density values.

Table 5: Evaluation of granules of Domperidone Maleate immediate release Layer

Formulation	Angle of repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index	Hausner Ratio
IR-1	29.31	0.54	0.62	12.90	1.14
IR-2	29.88	0.52	0.58	10.34	1.11
IR-3	30.26	0.56	0.64	12.5	1.14

Table 6: Evaluation of granules of Domperidone Maleate Sustained release Layer

Formulation	Angle of repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index	Hausner Ratio
SR-1	30.26	0.51	0.61	10.04	1.10
SR-2	31.46	0.54	0.60	9.45	1.16
SR-3	31.27	0.48	0.62	9.37	1.07
SR-4	30.87	0.52	0.59	10.14	1.09
SR-5	31.84	0.57	0.64	10.05	1.11
SR-6	31.09	0.56	0.60	9.57	1.08
SR-7	30.65	0.49	0.62	9.84	1.10
SR-8	30.05	0.56	0.63	9.96	1.04
SR-9	30.96	0.50	0.60	9.67	1.10

Evaluation of the tablets[22]

A) Physical Parameters

The compressed tablets were evaluated for thickness, average weight, hardness, weight variation and friability.

The results for SR Layer formulations SR-1, SR-2, SR-3, SR-4, SR-5, SR-6, SR-7, SR-8 & SR-9 are

Table 7: Evaluation of physical parameters of Domperidone Belayed Tablets

S. No.	Weight uniformity (mg)	Thickness (mm)	Disintegration test (sec)	Hardness (KP)	% Friability
SR-1	252.45	4.26	50	11.32	0.24
SR-2	251.97	4.27	45	12.83	0.31
SR-3	251.86	4.30	55	10.98	0.11
SR-4	249.94	4.23	48	13.65	0.21
SR-5	250.57	4.26	57	11.63	0.25
SR-6	251.78	4.27	35	12.86	0.23
SR-7	252.08	4.25	54	11.39	0.24
SR-8	250.85	4.26	60	13.68	0.15
SR-9	250.63	4.28	57	12.68	0.09

All the parameters are within the limits and found to be satisfactory in SR – 5 and the sample complies with respect to dissolution as per In-house specification

A) *In-vitro* dissolution studies

Table 8: Evaluation of In vitro dissolution of Domperidone Maleate IR Tablets

Time (mins)	IR 1	IR 2	IR 3
5	27.21	24.82	32.69
10	54.24	59.46	63.24
15	94.32	98.41	99.66

Table 9: Evaluation of In vitro dissolution of Belayed tablets of Domperidone Maleate

Time (hrs)	SR 1	SR 2	SR 3	SR 4	SR 5	SR 6	SR 7	SR 8	SR 9
0.5	5.92	8.13	7.75	8.13	5.91	7.45	10.84	5.52	7.44
1	11.53	11.16	11.84	11.16	9.55	10.89	16.74	9.07	10.84
2	24.17	17.12	20.24	17.12	15.86	19.29	27.76	14.00	17.88
3	37.05	30.23	27.21	30.23	27.91	29.21	40.57	20.24	24.82
4	50.05	44.61	32.21	44.61	41.22	35.24	50.05	30.46	30.07
5	55.59	54.17	39.49	54.17	46.57	41.49	67.58	37.53	35.40
6	66.37	59.20	45.35	59.20	54.25	48.35	80.09	39.70	41.92
7	76.66	67.22	54.24	65.22	62.77	55.32	99.61	45.21	48.41
8	87.56	76.46	60.42	74.46	71.97	60.42		49.08	54.13
9	98.52	84.57	66.51	82.57	78.59	65.51		57.10	63.24

Based on the in vitro release profile of drug from the formulations IR-1, IR-2, IR-3 in IR Portion and the formulations SR-1, SR-2, SR-3, SR-4, SR-5, SR-6, SR-7, SR-8, and SR-9 in SR portion, the formulation SR-5 was optimized for further studies. The formulation SR-5 showed better drug release, which was achieved by increasing the polymer concentration ratio of HPMC K100M to that of drug compared to formulation SR-2, and by adding HPMC K 100 M with Carbopol (extragranular) compared to the formulation SR-9. Hence the polymers in following ratios HPMC K4M (40%), HPMC K100 M (7.5%) and HPMC K 100M (10%) with Carbopol (3%) released the drug in a controlled rate at regular time intervals in appropriate concentrations as per the limits. Hence the formulation F-5 was selected for further studies.

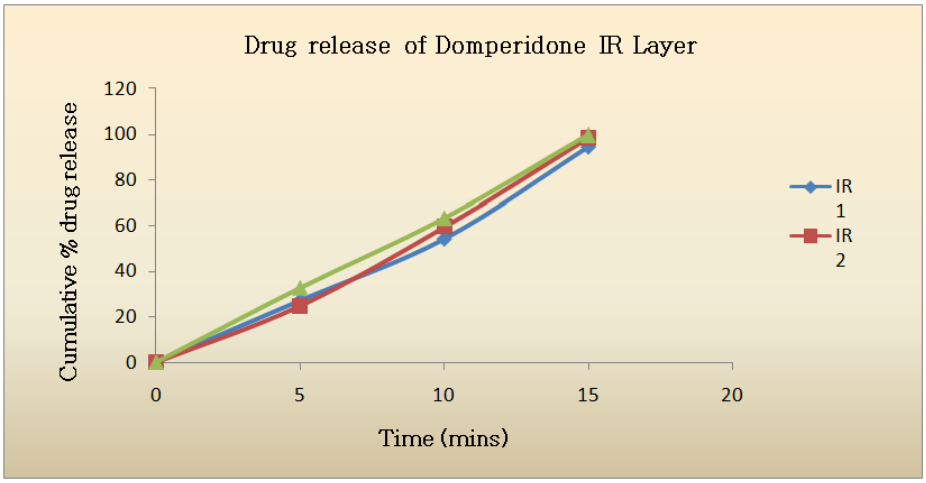


Fig. 6: Comparision of cumulative percentage Drug release of different formulations of Belayed tablets.

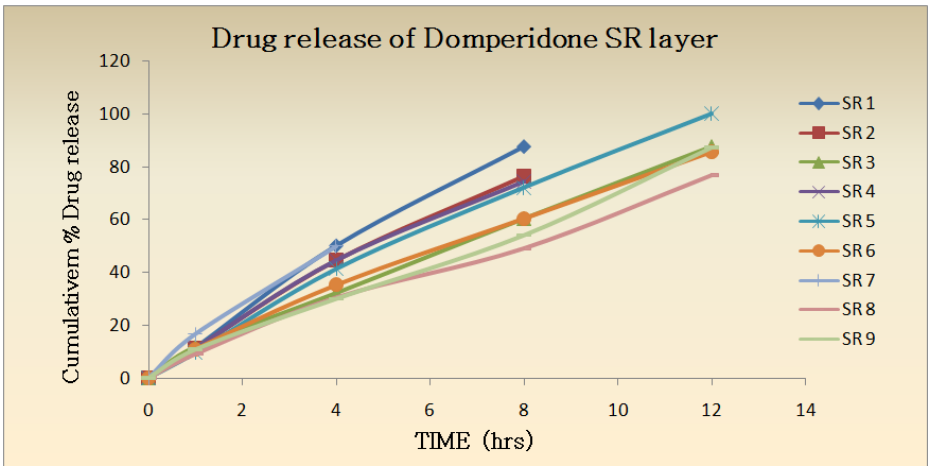
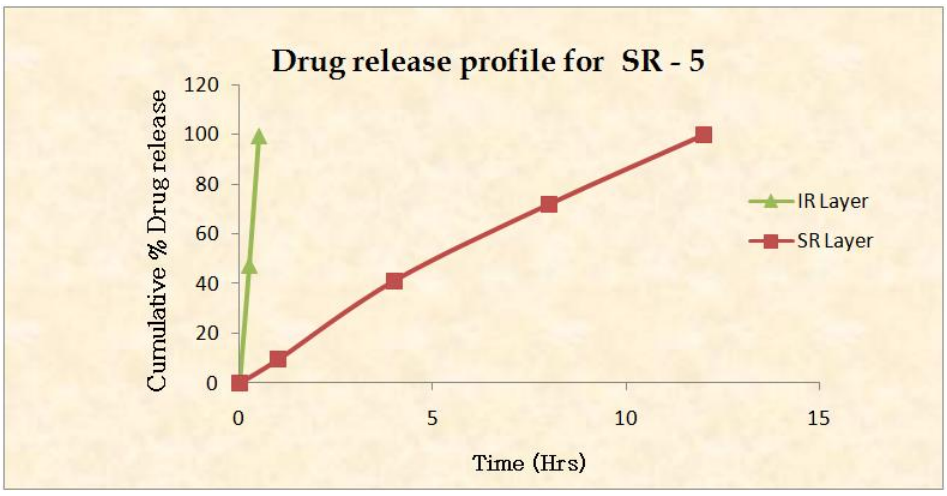


Fig. 7: CPR of Different Formulations of Domperidone SR layer



Mathematical model fitting of obtained drug release data:[25,26]

The in-vitro release studies data was quantified to determine the release mechanism, to fit various mathematical models and to determine which was the best-fit model. The various par ameters like the time exponent (n), the release rate constant (k) and the regression co-efficient (R^2) were also calculated. In a set of data, the model showing the highest value to $R^2$was taken as the best-fit model.

In the tables

R^2= Regression coefficient.

n = Time exponent.

K = release rate constant

Table 10: Data of various parameters of model fitting for Domperidone Maleate for optimized formulation F – 5

Formulation	Zero Order	First Order	Higuchi	Peppas	
F – 5	R^2	R^2	R^2	R^2	K
	0.992	0.849	0.954	0.995	0.949

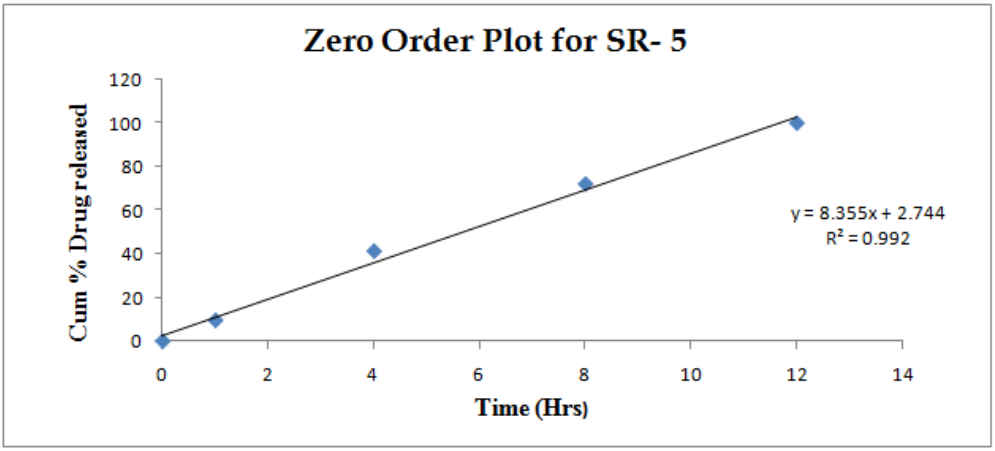


Fig. 7: Plot showing zero order kinetics of formulation SR-5.

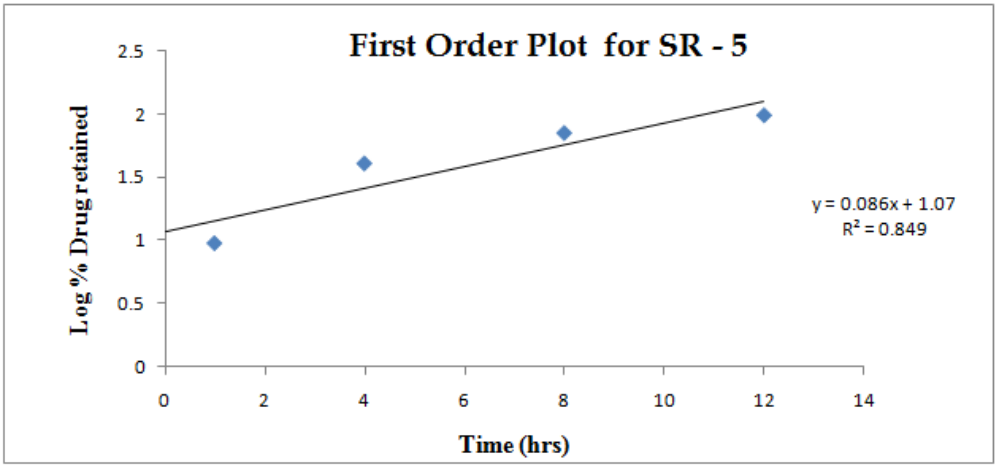


Fig. 8: Plot showing First order kinetics of formulation SR-5.

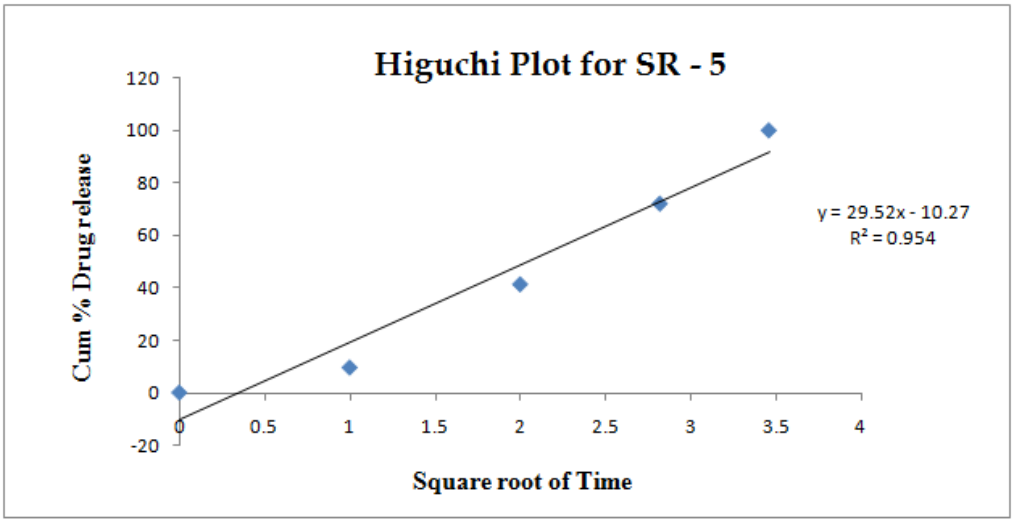


Fig. 9: Plot showing Higuchi Model of formulation SR-5.

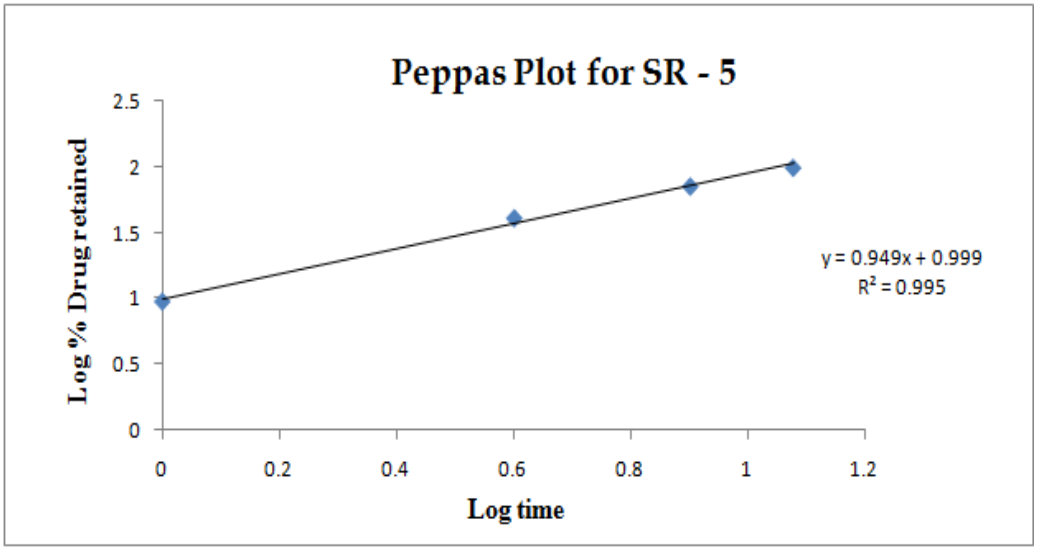


Fig. 10: Plot showing Peppas Plot of formulation SR-5.

CONCLUSION

From the Preformulation studies API (Active Pharmaceutical Ingredient) characterization, and drug-excipient compatibility studies were carried out. The API characterization showed compliance with the drug characteristics.The polymers and other excipients were selected based on the satisfying results produced during drug-excipient compatibility studies to develop the final formulation. The in vitro study showed that formulation SR - 5 was ideally suited to be sustained release formulation.The final suitable formulation was achieved fruitfully by the wet granulation method for layer 1 and layer 2. HPMC K 100 M at a concentration of 7.5%, produced desired release profile for Domperidone Maleate sustained release layer as per in-house specifications The results reveal that trial SR- 5 has met the objective of sustained drug release, patient convenience and cost effectiveness as a twice a day dose of the drug. Success of the In vitro drug release studies recommends the product for further in vivo studies, which may improve patient compliance .From the literature Domperidone Maleate, individual dosage form was used in the management of Emesis. Combination of immediate release layer and sustained release layer improves the patient compliance.From the results formulation SR -5 has been selected as best formulation among all the other formulations. Formulation SR – 5 provides better in vitro release from layer 1 as well as layer 2. The data obtained from in vitro release study were fitted to various mathematical model like zero order, First order, Higuchi model and Peppas model. The results of mathematical model fitting of data obtained indicated that, the best fit model in all the cases the release was found to be by diffusion and nonfickian release.

REFERENCES

1. Lehman .L L A. Herbert, Kanig, L. Joseph. The theory and Practice of Industrial Pharmacy. 1987;3rd Edition: 293.
2. Jain,N.K S.N. Sharma. Vallabh Prakashan. A Text book professional pharmacy.
3. Gilbert S. Banker, Neil R. Anderson. Tablets. In Leon Lachman, Herberta Liebermann, Joseph L Kanig. (Edition), the theory and practice of Industrial pharmacy, 3rd Ed. Lea and Febiger, Philadelphia, 1987, [a] 293-294, [b] 330-331, [c] 430-431.
4. Abraham. M.A., Shirwaikar. A., Formulation of multilayered sustain release tablets using insoluble matrix system., Indian Journal of Pharmaceutical Science. 1997 59[6]: 312-315.
5. Timmins, Biphasic controlled release system for high solubility pharmaceuticals and method. United States Patent 64,75,521.5th November 2002.
6. Ziyaur R Mushir A.R.K. Formulation and evaluation of bilayer floating tablets of captopril. *Acta Pharm.* 2006; 56:49-57.
7. Narendra C, Srinath MS, Babu G. Evaluation of Belayed Floating Tablet Containing Metoprolol Tartrate as a Drug for Gastric Retention. *AAPS PharmSciTech*. 2006; 7[2]: Article 34. DOI: 10.1208/pt070234.
8. Patel VM, Prajapati BG, Patel HV, Patel KM. Mucoadhesive Belayed Tablets of Propranolol Hydrochloride. *AAPS PharmSciTech.* 2007; 8[3]: Article 77. DOI: 10.1208/pt0803077.
9. Vogeleer.J, Bi-layer tablets – why special technology is required the Courtoy-R29F tablet press, designed for quality bi-layer tablets Nitro Pharma Systems.
10. Ryan.K, *et al* Multi-layer tableting Q&A-Press manufacturers weigh in on multi-layer tabletting's advantages misconceptions, and future.
11. Ramana RG, *et al.,* Spectrophotometric estimation of Acebutalol hydrochloride and Domperidone in their dosage forms. The Eastern Pharmacist 1990 May; 133-135.
12. Kusum Devi, *et al...* A Novel technique for the preparation of Mouth dissolving tablets of Domperidone. Indian drugs 2003; 40[9]: 544-546.
13. Takahashi t, *et al.* Mechanism for the gastrokinetic action of domperidone. In vitro studies in guinea pigs; A Technical note. AAPS Pharma Sci Tech 2003; 4[4]; Article 70
14. Arnold.G, *et al.,* Domperidone is superior to ondansetron in acute apomorphine challenge in previously untreated parkinsonian patients - A double blind study. Indian J Pharm Sci 2004; 66[3]; 350-353.
15. Neijt .J.P, *et al.,* Buprenorphine versus domperidone in chemotherapy-induced emesis: A pilot study. Indian Drugs 2004; 41[9]; 554-557.
16. Ramprakash.G, *et al.,* Design, optimization and evaluation of Domperidone coevaporates.International Journal of Pharmaceutical Sciences 160 [1998], p. 251
17. Jadoul.A, V,Préat. Electrically enhanced transdermal delivery of domperidone. International Journal of Pharmaceutical Research and Development.2009 Nov, 34[16].
18. DOMPERIDONE MALEATE – world health organization – Final text for addition to the International Pharmacopoeia, document QAS/05.145/FINAL March 2009.
19. Rowe, Paul J.S and Sian C.O. Handbook of Pharmaceutical Excipients Fifth edition [2006], Published by the pharmaceutical press publications division of the Royal Pharmaceutical Society of Great Britain, UK.
20. Leon Lachman, Herbert A. Lieberman: Granulation properties in "the theory and practice of industrial pharmacy" Varghese publishing house: 3: 315-317.
21. Copper J gin C.Turtorial Pharmacy, Powder flow and compaction. In carter SJ. New Delhi: CBS publication and distributors: 1986; 6:211-213.

22. Evaluation of Tablets as per "B.P 2009" appendix 7-3: A-82-A-83.
23. Subramanyam CVS, Text book of Physical Pharmaceutics 2nd edition, New Delhi; Vallabh prakashan; 2001.
24. Alfred Martin, Physical Pharmacy-physiochemical principles in the pharmaceutical sciences. 4th edition New Delhi: B.I Waverly Pvt. Ltd; 1996:313-316.
25. Sipemann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Del Rev 2001; 48: 139-57.
26. Higuchi S, Itoi C, Nishigaki S, Sakai N. nonlinear renormalization group equation of matrix models. Tokyo institute of technology preprint TIT/HEP- 228, NUP-A-93-13[1993].