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FORMULATION AND *INVITRO* EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF DOMPERIDONE

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Abstract:

In the present work, an attempt has been made to develop controlled release tablets of Domperidone by selecting different grade of HPMC like HPMC K4 M, HPMC K15 M and Eudragit S-100 as retarding polymers. All the formulations were prepared by direct compression method. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Dissolution studies of Domperidone controlled release tablets in media with different dissolution media 0.1N HCl, Phosphate buffer pH (6.8) as per US Pharmacopoeia. The dissolution data revealed that the ratio of polymers is very important to achieve an optimum formulation. The formulation of Domperidone CR tablets shown that formulation F6 with HPMC K4 M (10mg) shown good drug release profile. Among all the formulations F6 formulation showed maximum % drug release i.e., 99.36% in 12 hours hence it is considered as optimized formulation F6 which contains HPMC K4 M (10mg).

Keywords: *Domperidone, HPMC K4 M, HPMC K15 M, Eudragit S-100 and controlled release tablets.*

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INTRODUCTION:

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, convenient and safe due to its ease of administration, patient acceptance, and cost effective manufacturing process. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. [1,2,3]

Controlled release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ. Greater attention is paid on development of oral controlled release drug delivery systems due to flexibility in designing of dosage form. The main challenges to oral drug delivery systems are to deliver a drug at therapeutically effective rate to desirable site, modulation of GI transit time and minimization of first pass elimination. Control release dosage form provides better maintenance of optimal and effective drug level for prolonged duration with less dosing frequency and side effects. [4,5]

Historically, oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact the gastrointestinal physiology offers more flexibility in dosage form design than most other routes A major challenge for the pharmaceutical industry in drug development is to produce safe and efficient drugs, therefore properties of drugs and the way in which they are delivered must be optimised.

A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels. Drug release is dependent on polymer properties, thus the application of these properties can produce well characterised and reproducible dosage forms. [6]

The basic rationale of a controlled release drug delivery system is to optimize the biopharmaceutics, pharmacokinetics, and pharmacodynamics properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of disease condition in the shortest possible time by using smallest quantity of drug, administered by most suitable route. The immediate release drug delivery system lacks some features like dose maintenance, controlled release rate and site targeting. An ideal drug delivery system should deliver the drug at a rate dictated by the need of body over a specified period of treatment.

A controlled release drug delivery system is capable of achieving the following benefits over conventional dosage forms:

- Total dose is low.
- Reduced GI side effects and other toxic effects.
- Reduced dosing frequency.
- Better patient acceptance and compliance.
- Less fluctuation in plasma drug levels.
- More uniform drug effect.
- Better stability of drug. [7]

Advantages of Controlled Release Drug Delivery System:

1. Therapeutic advantage: Reduction in drug plasma level fluctuation, maintenance of a steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug.
2. Reduction in adverse side effects and improvement in tolerability: Drug plasma levels are maintained within a narrow window with no sharp peaks and with AUC of plasma concentration Vs time curve comparable with total AUC from multiple dosing with immediate release dosage form.
3. Patient comfort and compliance: Oral drug delivery is the most common and convenient for patient and a reduction in dosing frequency enhances compliance.
4. Reduction in Health care cost: The total cost of therapy of the controlled release product could be comparable or lower than the immediate release product with reduction in side effects. The overall expense in disease management also would be reduced. This greatly reduces the possibility of side effects, as the scale of side effects increases as we approach the maximum safe concentration.

Avoid night time dosing: It also good for patients to avoid the at night time.[8,9,10]

Disadvantages:

1. Dose dumping: Dose dumping is a phenomenon whereby relatively large quantity of drug in a controlled release formulation is rapidly released, introducing potentially toxic quantity of the drug into systemic circulation. Dose dumping

can lead to fatalities in case of potent drugs, which have a narrow therapeutic index.

2. Less flexibility in accurate dose adjustment: In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of controlled release dosage forms, this appears to be much more complicated. Controlled release property may get lost, if dosage form is fractured.
3. Poor In-vitro In-vivo correlation: In controlled release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so- called 'absorption window' becomes important and may give rise to unsatisfactory drug absorption in-vivo despite excellent in-vitro release characteristics.
4. Increased potential for first pass clearance: Hepatic clearance is a saturable process. After oral dosing, the drug reaches the liver via portal vein. The concentration of drug reaching the liver dictates the amount metabolized. Higher the drug concentration, greater is the amount required for saturating anenzyme surface in the liver. Conversely, smaller the concentration found with the controlled release and a sustained release dosage form, lesser is the possibility of saturating the enzyme surface. The possibility of reduced drug availability due to the first pass metabolism is therefore greater with controlled release and sustained released formulation than with conventional dosage form.
5. Patient variation: The time period required for absorption of drug released from the dosage form may vary among individuals. Co-administration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patients.
6. Administration of controlled release medication does not permit prompt termination of therapy. Immediate changes in drug levels during therapy, such as might be encountered if significant adverse effects are noted, can not be accommodated.
7. There is danger of an ineffective action or even absence of it if the therapeutic substance is poorly absorbed from GIT.
8. Therapeutic agents for which single dose exceeds 1 gm, the technical process requirements may make te product very difficult or sometimes impossible to prepare.
9. Therapeutical agents which absorbed by active transport are not good candidates for controlled release dosage form e. g. Riboflavin.
10. Economic factors must also be taken into account, since more costly processes and equipments are involved in manufacturing of many controlled release dosage forms. [11]

Factor Influencing the Formulation of Oral Controlled Release Drug Delivery System:

Physicochemical Factors:

Solubility:

Low aqueous solubility drugs have low oral bioavailability. Drugs having good solubility in stomach are poor choice for controlled/sustained oral dosage forms. The water solubility limits the loading efficiency of drug into a variety of carrier systems such as liposome and micro particles, where highly water-soluble drug tend to leach fast from the carrier. The pH dependent solubility particularly in the physiological pH rangewould be another problem for controlled release formulation because of the variation in pH throughout the gastrointestinal tract and variation in the dissolution rate. The biopharmaceutical classification system allow to estimate contribution of three major factors Solubility, Dissolution and Intestinal Permeability which affect oral absorption. Class III (High solubility-Low permeability) and Class IV (Low solubility-Low permeability) drugs is poor candidate for controlled release dosage form.

Drug Stability:

A drug in a solid state undergoes degradation at a much slower rate than a drug in suspension or solution6,. Drugs that are unstable in gastric pH can be developed as slow release dosage form and the drugs can be delayed till the dosage form reaches the intestine. Drugs that undergo gut-wall metabolism and show instability in small intestine are not suitable for oral controlled drug delivery systems.

Molecular Size and Diffusivity:

Diffusivity defined as the ability of a drug to diffuse through membrane, is inversely related to molecular size. Diffusivity depends on size and shape of the cavities of the membrane. More than 95% of drugs are absorbed by passive diffusion. The upper limit of drug molecular size for passive diffusion is 600 Dalton. The examples of the drugs which are difficult to control release rate of medicament from dosage form are proteins and peptides.

Partition coefficients:

Partition coefficient id defined as the fraction of drug in an oil phase to that of an aqueous phase. It governs the permeation of drug particles through biological membrane. Drugs with high partition coefficient value easily permeate through biological membrane.

The diffusion of drug molecules across rate controlling membrane or through the matrix system essentially relies on partition coefficient. Drugs that have lower partition coefficient are not suitable for oral controlled release drug delivery system and drugs that have higher partition coefficient are also not suitable for oral controlled drug delivery system because they will not partition out of the lipid membrane once it gets in the membrane.

Drug pKa and ionization at physiological pH:
Drugs existing largely in ionized form are poor candidate for oral controlled release drug delivery system because absorption rate of ionized drug is 3-4 times less than that of unionized form. The pKa range for acidic drug whose ionization is pH sensitive is around 3.0-7.5 and for basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption.

MATERIALS:

Domperidone SURA LABS, Eudragit S 100 Merck Specialities Pvt Ltd, Mumbai, India, HPMC K4 M Merck Specialities Pvt Ltd, Mumbai, India, HPMC K15 M Merck Specialities Pvt Ltd, Mumbai, India, PVP K30 Merck Specialities Pvt Ltd, Mumbai, India, Mg-Stearate Merck Specialities Pvt Ltd, Mumbai, India, Talc Merck Specialities Pvt Ltd, Mumbai, India, MCC Merck Specialities Pvt Ltd, Mumbai, India

METHODOLOGY:

Analytical method development:
Determination of absorption maxima:
100mg of Domperidone pure drug was dissolved in 100ml of Methanol (stock solution) 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml) and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Preparation calibration curve:
100mg of Domperidone pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 5,10,15,20 and 25 µg/ml of Rivastigmine per ml of solution. The absorbance of the above dilutions was measured at 255nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Table1: Formulation composition for tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Domperidone	10	10	10	10	10	10	10	10	10	10	10	10
Eudragit S 100	5	10	15	20	-	-	-	-	-	-	-	-
HPMC K4 M	-	-	-	-	5	10	15	20	-	-	-	-
HPMC K15 M	-	-	-	-	-	-	-	-	5	10	15	20
PVP K30	10	10	10	10	10	10	10	10	10	10	10	10
Mg-Stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	4	4	4	4	4	4	4	4	4	4	4	4
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total Weight	80	80	80	80	80	80	80	80	80	80	80	80

All the quantities were in mg

RESULTS AND DISCUSSION:

Standard Calibration curve of Domperidone:

Table2: Concentration and absorbance obtained for calibration curve of Domperidone in 0.1 N hydrochloric acid buffer (pH 1.2**)**

S. No.	Concentration (µg/ml)	Absorbance* (at 255 nm)
1	0	0
2	10	0.148
3	20	0.284
4	30	0.411
5	40	0.538
6	50	0.667

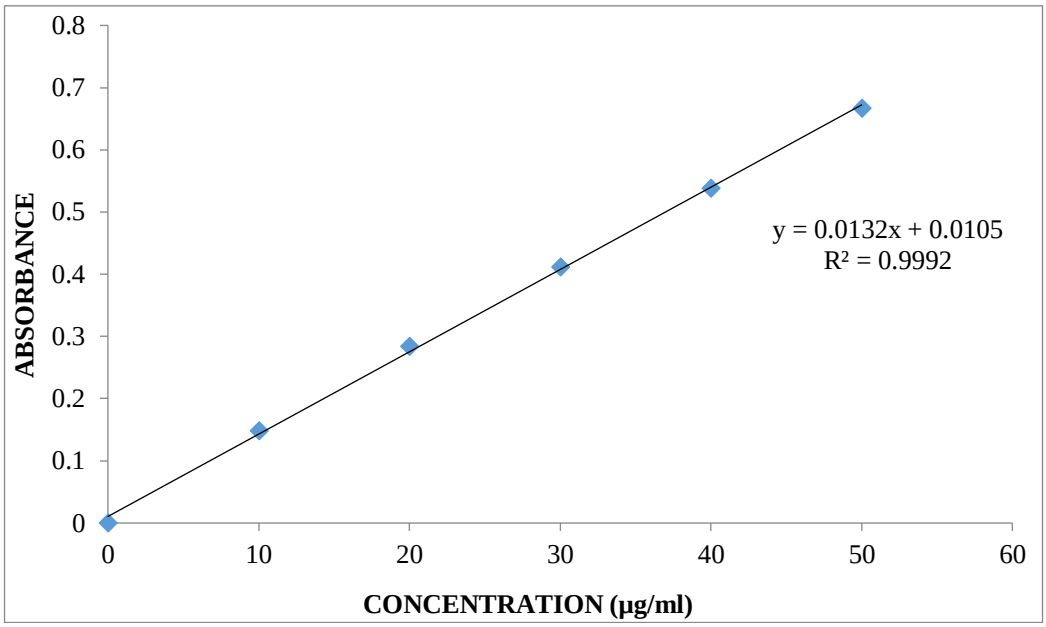

Fig 1 : Standard graph of Domperidone in 0.1 N HCl

Table3 Concentration and absorbance obtained for calibration curve of Domperidone in pH 6.8 Phosphate buffer.

S. No.	Concentration (µg/ml)	Absorbance* (at 257 nm)
1	0	0
2	5	0.135
3	10	0.259
4	15	0.398
5	20	0.518
6	25	0.634

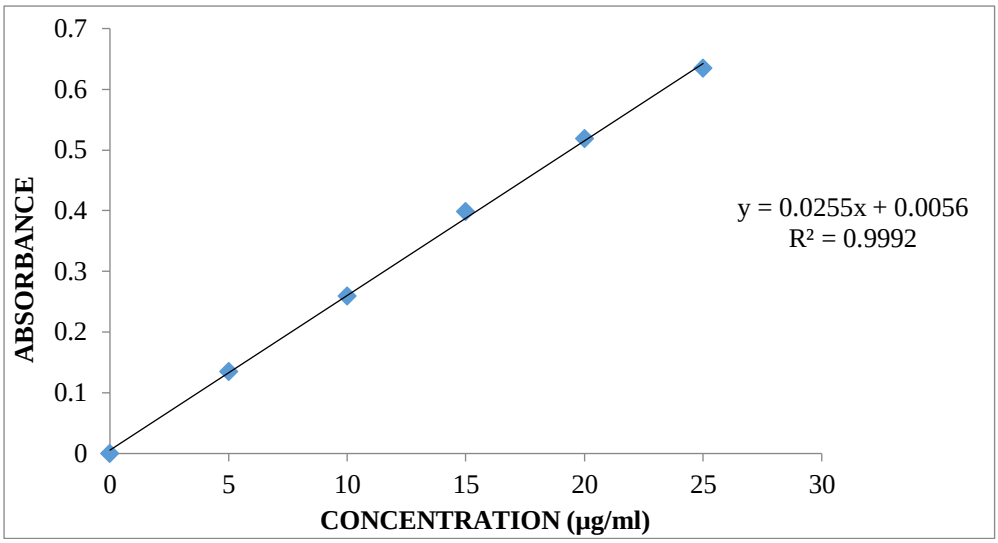

Fig2: Standard graph of Domperidone in pH 6.8 Phosphate buffer

Preformulation parameters of powder blend:

Table 4 Pre-compression parameters

Formulations	Formulations	Formulations	Formulations	Formulations	Formulations
F_1	F_1	F_1	F_1	F_1	F_1
F_2	F_2	F_2	F_2	F_2	F_2
F_3	F_3	F_3	F_3	F_3	F_3
F_4	F_4	F_4	F_4	F_4	F_4
F_5	F_5	F_5	F_5	F_5	F_5
F_6	F_6	F_6	F_6	F_6	F_6
F_7	F_7	F_7	F_7	F_7	F_7
F_8	F_8	F_8	F_8	F_8	F_8
F_9	F_9	F_9	F_9	F_9	F_9
F10	F10	F10	F10	F10	F10
F11	F11	F11	F11	F11	F11
F12	F12	F12	F12	F12	F12

All the values represent n=3

Quality control parameters for tablets:

Table5: Post compression parameter:

Formulation codes	Weight variation(mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	80.2	5.2	0.58	1.15	96.36
F2	80.1	5.1	0.49	1.36	98.10
F3	78.4	6.3	0.50	1.87	96.91
F4	80.2	6.0	0.69	1.10	97.62
F5	79.6	5.0	0.48	1.25	95.31
F6	78.8	5.8	0.55	1.31	99.81
F7	80.0	6.2	0.57	1.10	98.72
F8	80.1	6.3	0.63	1.11	97.87
F9	79.9	5.3	0.47	1.08	96.21
F10	78.6	5.9	0.65	1.12	95.12
F11	79.5	6.7	0.59	1.09	99.32
F12	80.0	5.6	0.66	1.44	98.98

***In Vitro* Drug Release Studies**

Table6: *In -vitro* dissolution data

Time(Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	10.15	7.11	7.86	6.87	8.61	13.14	5.35	9.32	15.32	13.11	11.32	9.87
1	19.54	12.54	11.8	10.85	12.51	15.32	12.71	10.47	19.23	15.88	13.82	10.96
2	27.74	24.41	21.25	17.55	15.87	24.31	16.32	18.32	25.61	20.74	20.71	17.21
3	35.65	32.42	29.51	25.36	21.32	31.74	24.71	23.85	31.84	26.47	24.98	21.52
4	45.28	45.98	36.85	32.74	32.85	43.89	33.85	35.63	35.54	37.11	30.21	27.54
5	54.32	57.16	40.87	41.25	43.87	51.64	42.13	46.25	41.87	43.69	36.87	33.31
6	63.19	64.65	47.27	47.85	47.27	58.99	48.87	52.85	49.98	51.31	41.92	40.28
7	79.58	71.26	51.32	53.87	52.25	67.41	55.47	58.36	55.74	57.39	56.39	46.27
8	85.92	77.35	63.13	63.85	60.32	76.52	66.52	69.81	61.87	65.74	61.11	59.62
9	88.93	85.74	73.25	72.87	69.95	85.87	73.21	76.99	71.33	75.98	68.84	64.49
10	94.14	87.25	83.47	79.87	73.12	91.74	79.31	84.14	77.25	81.28	78.74	76.68
11	96.18	94.87	89.59	83.19	83.31	95.11	85.84	89.31	85.52	87.57	83.47	80.59
12	97.74	96.99	94.25	93.25	95.74	**99.36**	92.95	95.14	92.95	94.38	91.89	90.78

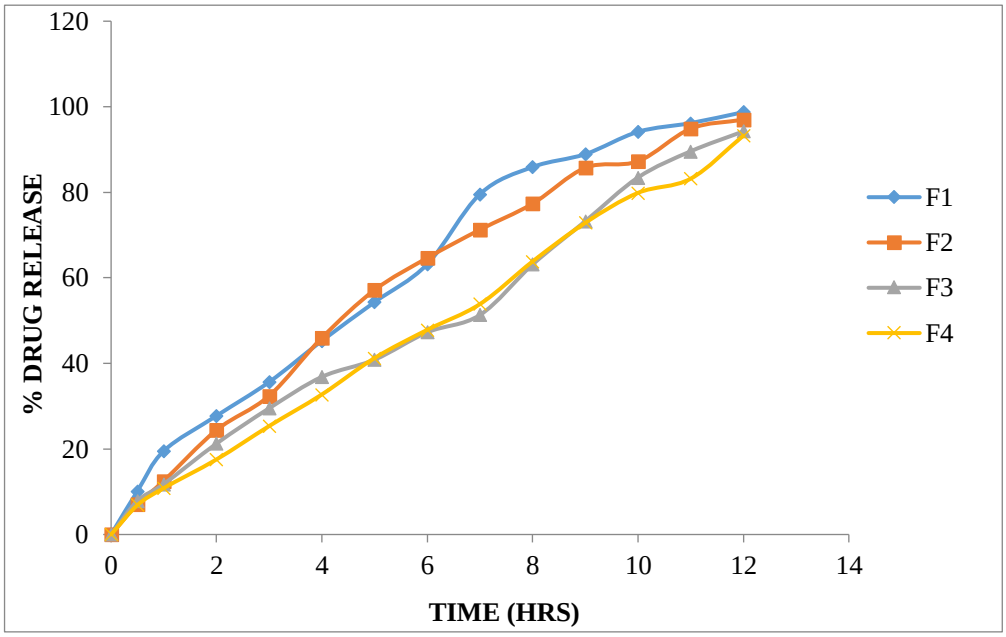

Fig3: Dissolution profile of formulations prepared with Eudragit S 100 polymer

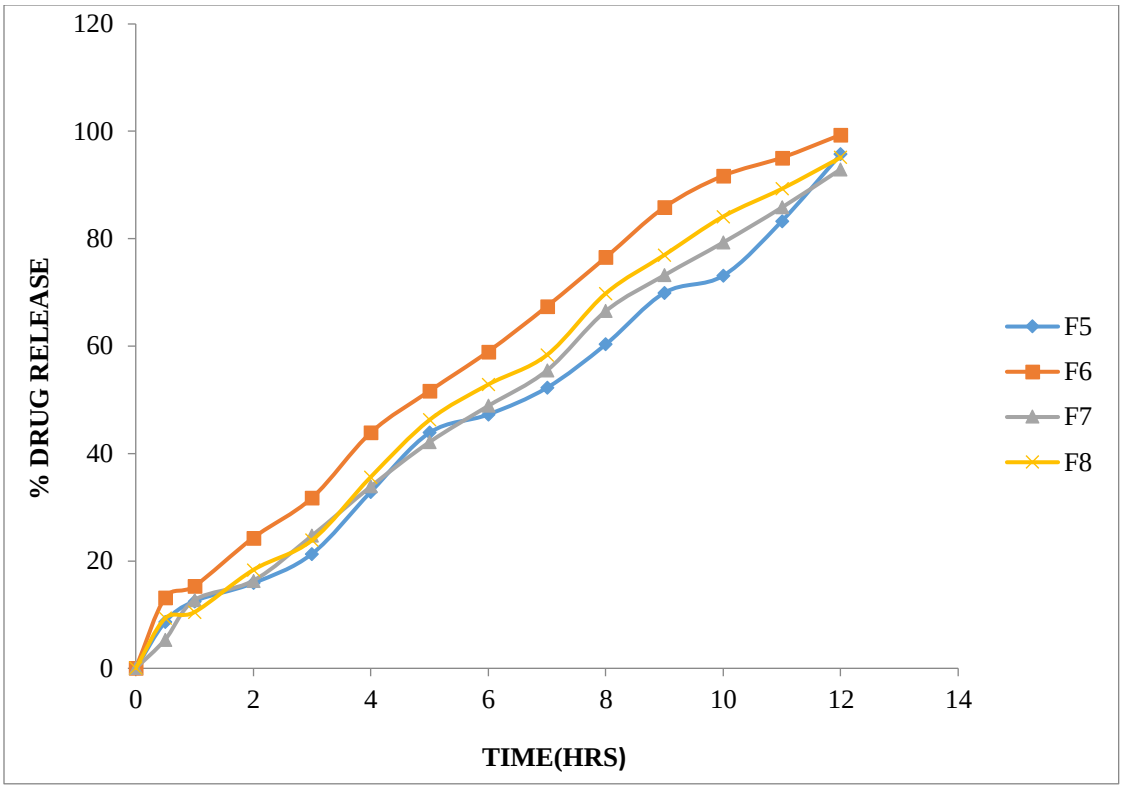

Fig4 : Dissolution profile of formulations prepared with HPMC K4 M polymer

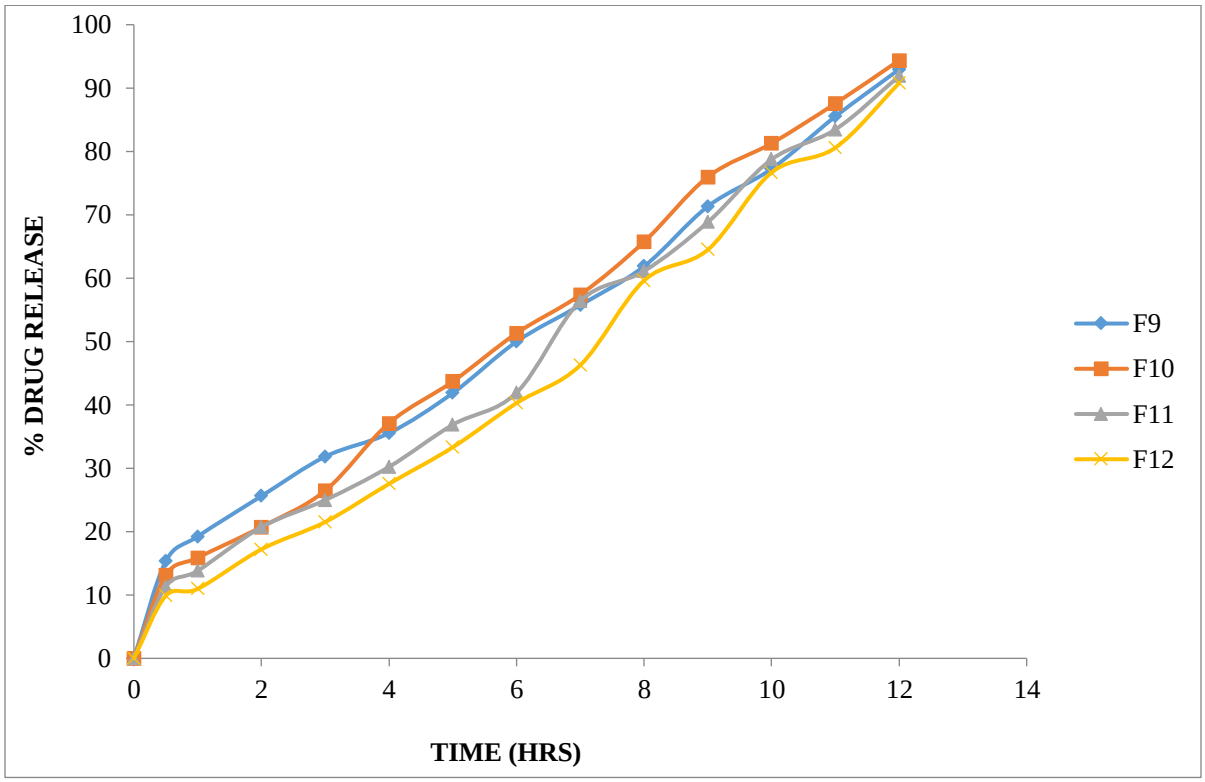

Fig5 : Dissolution profile of formulations prepared with HPMC K15 M as polymer

Table 7:Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
13.14	0.5	0.707	1.119	-0.301	1.939	26.280	0.0761	-0.881	86.86	4.642	4.429	0.213
15.32	1	1.000	1.185	0.000	1.928	15.320	0.0653	-0.815	84.68	4.642	4.391	0.250
24.31	2	1.414	1.386	0.301	1.879	12.155	0.0411	-0.614	75.69	4.642	4.230	0.412
31.74	3	1.732	1.502	0.477	1.834	10.580	0.0315	-0.498	68.26	4.642	4.087	0.555
43.89	4	2.000	1.642	0.602	1.749	10.973	0.0228	-0.358	56.11	4.642	3.828	0.813
51.64	5	2.236	1.713	0.699	1.684	10.328	0.0194	-0.287	48.36	4.642	3.643	0.998
58.99	6	2.449	1.771	0.778	1.613	9.832	0.0170	-0.229	41.01	4.642	3.448	1.193
67.41	7	2.646	1.829	0.845	1.513	9.630	0.0148	-0.171	32.59	4.642	3.194	1.447
76.52	8	2.828	1.884	0.903	1.371	9.565	0.0131	-0.116	23.48	4.642	2.864	1.778
85.87	9	3.000	1.934	0.954	1.150	9.541	0.0116	-0.066	14.13	4.642	2.418	2.224
91.74	10	3.162	1.963	1.000	0.917	9.174	0.0109	-0.037	8.26	4.642	2.021	2.620
95.11	11	3.317	1.978	1.041	0.689	8.646	0.0105	-0.022	4.89	4.642	1.697	2.944
99.36	12	3.464	1.997	1.079	-0.194	8.280	0.0101	-0.003	0.64	4.642	0.862	3.780

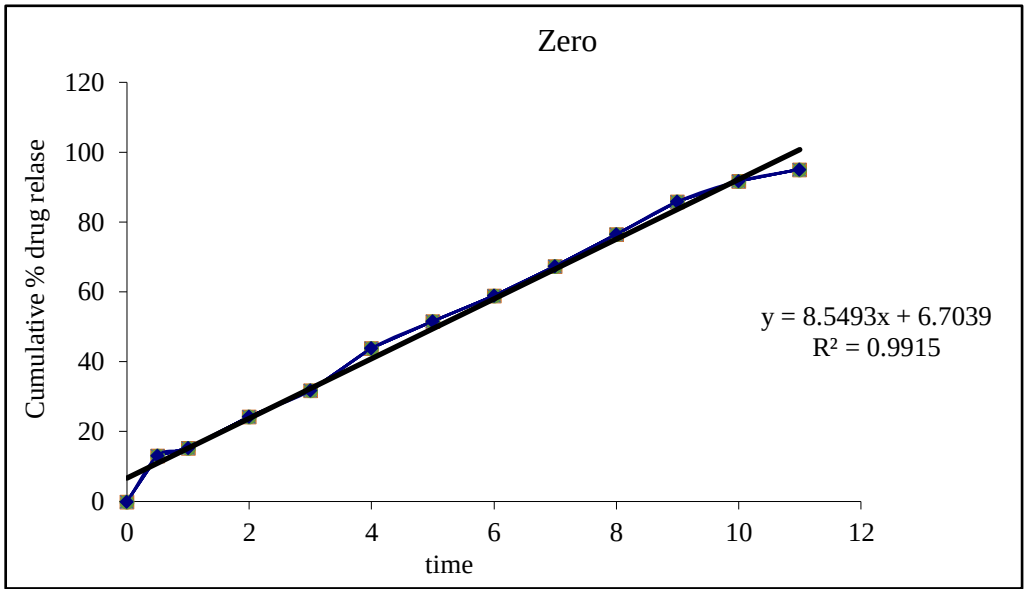

Fig 6: Zero order release kinetics graph

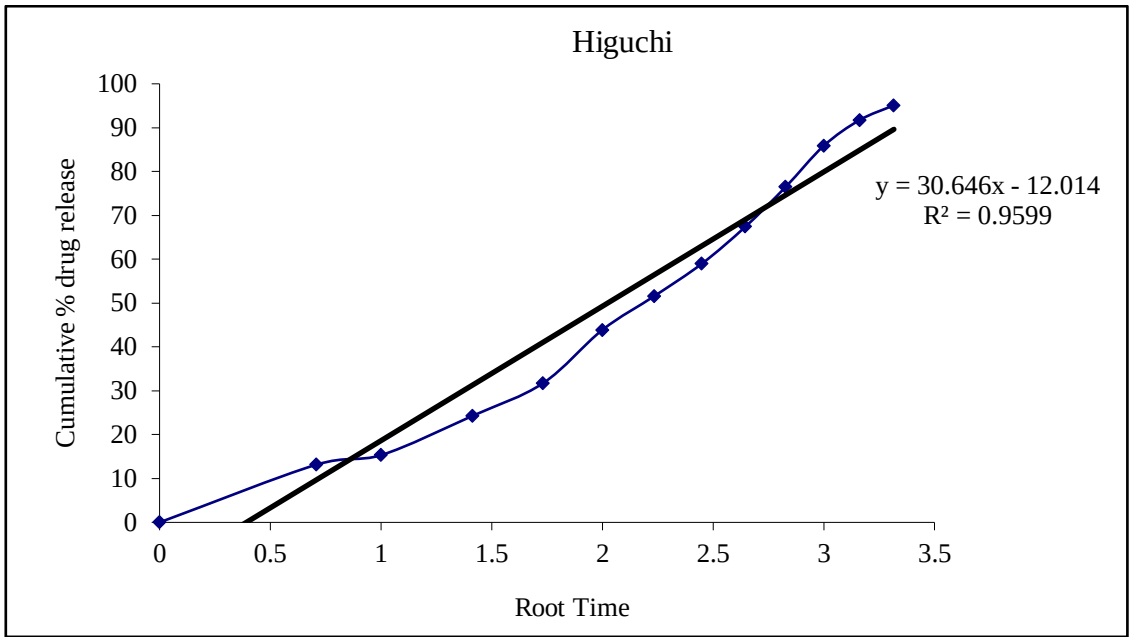

Fig 7 : Higuchi release kinetics graph

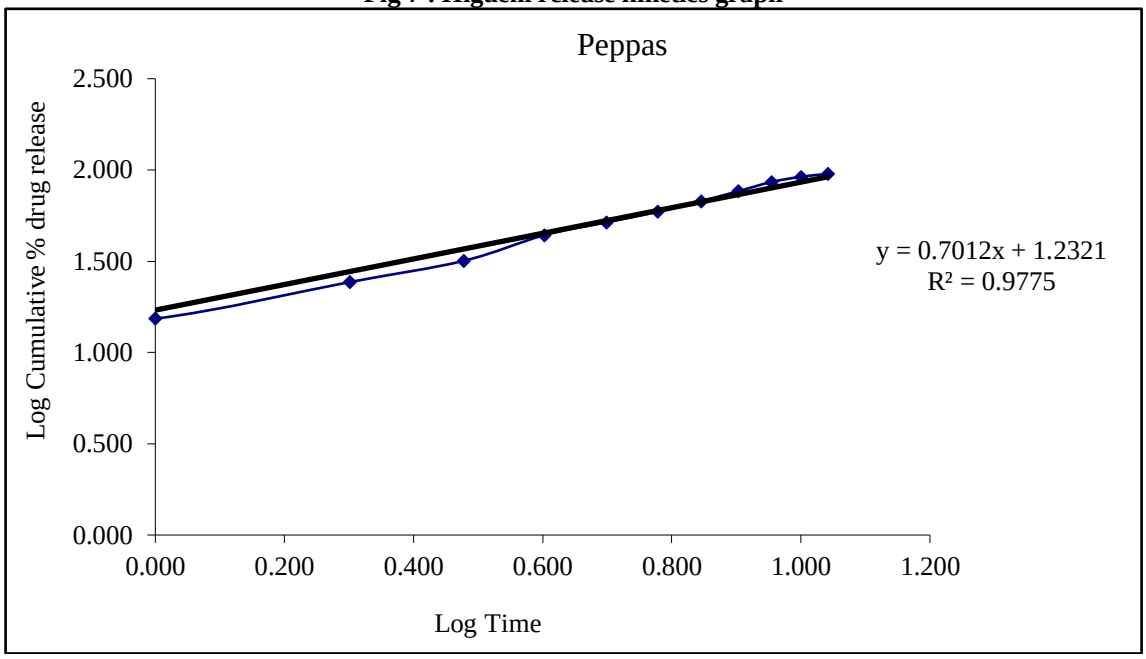

Fig8 : Kars mayer peppas graph

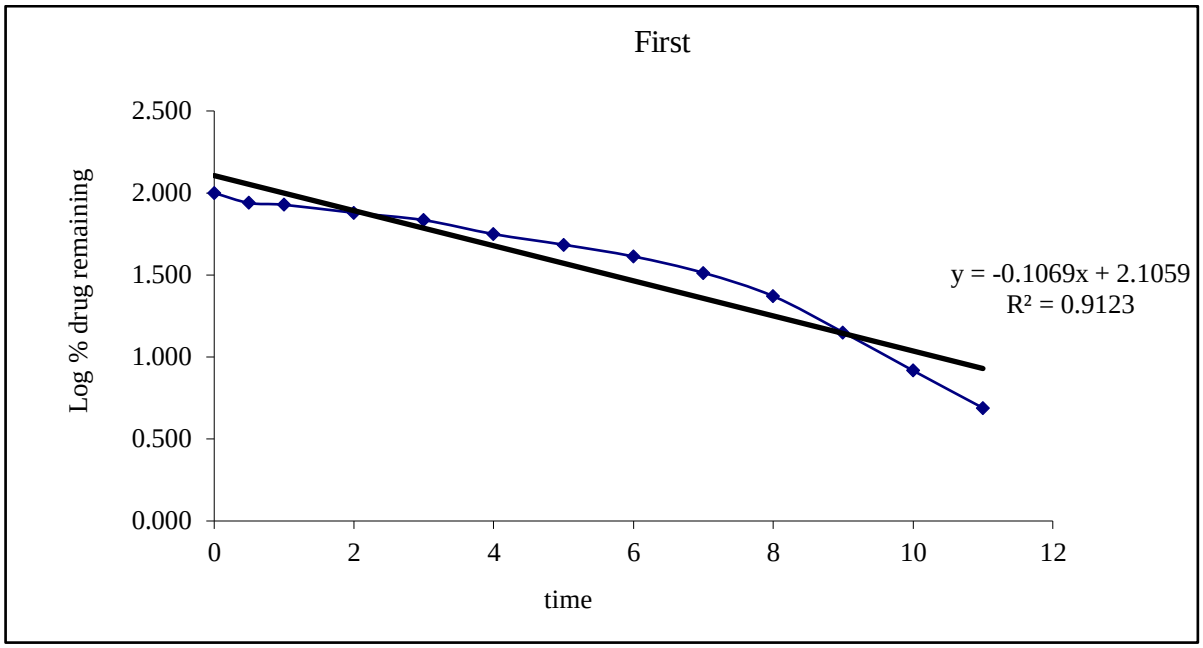

Fig9 : First order release kinetics graph

Drug – Excipient compatibility studies

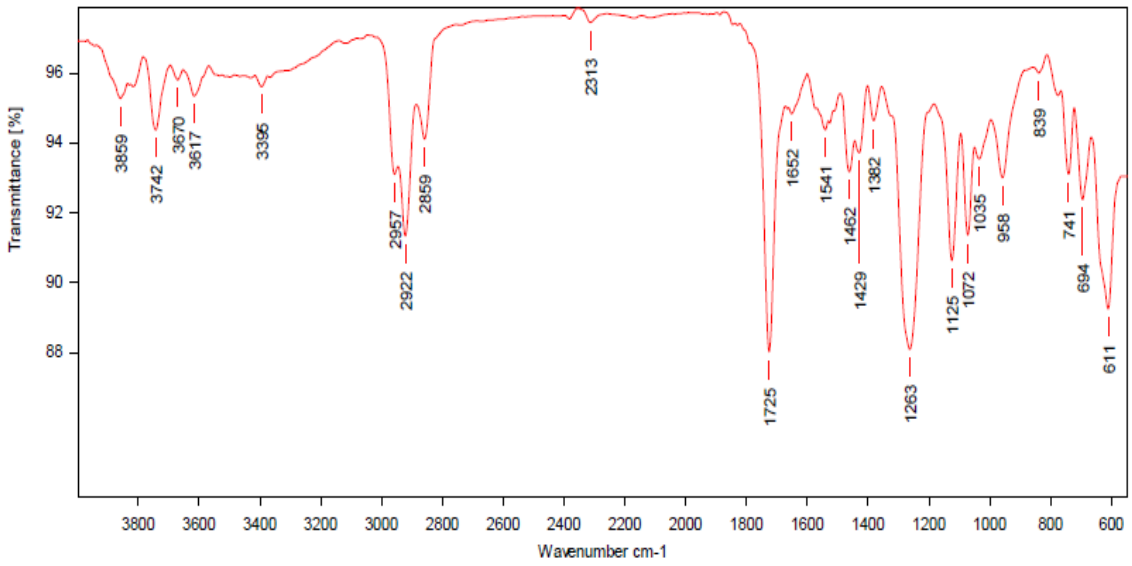

Fig no10: FT-TR Spectrum of Domperidone pure drug

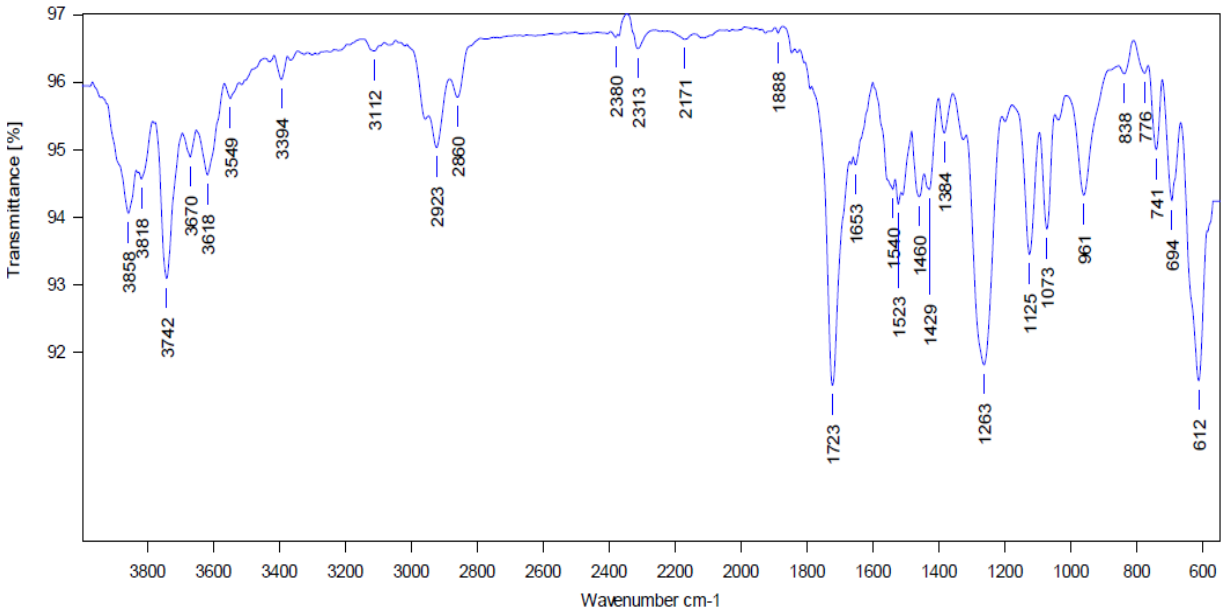

Fig No 11:FT-IR Spectrum of Optimised Formulation

CONCLUSION:

In the present work, an attempt has been made to develop controlled release tablets of Domperidone by selecting different grades of HPMC like HPMC K4 M, HPMC K15 M and Eudragit S-100 as retarding polymers. FTIR studies revealed that there was no chemical interaction between drug and other excipients. All the formulations were prepared by direct compression method. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F6 formulation showed maximum % drug release i.e., 99.36% in 12 hours hence it is considered as optimized formulation F6 which contains HPMC K4 M (10mg). To analyze the mechanism of drug release from the tablet, the *in-vitro* drug release data were fitted to Zero order, First order, Higuchi and Korsmeyer-Peppas model. It was observed that the release of drug followed Zero order release kinetics.

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