Formulation, Development and Optimization of Floating Sustain Release Tablets of Domperidone for the Effective Treatment of Antiemetic During Chemotherapy

Rohit Kumar[1], Ashutosh Tripathi[2]
[1,2]*IIMT College Knowledge Park-3 Gr. Noida, Uttar Pradesh*

Abstract **- Objective- Formulation Development and optimization of Domperidone SR floating tablets for treatment of chemotherapy patient for continued emesis & maintaining a certain concentration of the administered a drug over a specific period of time into the patients system while reducing possible side effects.**
METHOD- The wet-granulation process was utilised to enhance the formulation of oral floating SR tablets. In this work, we created gastroretentive floating SR tablets for Domperidone using three distinct polymers: HPMC K4M, HPMC K15M, and HPMC K100M. The goal of this study is to enhance and assess the in vitro and in vivo performance of manufactured floating SR tablets.
RESULT- The produced tablets were analysed and found to have excellent physicochemical properties. The effects of different HPMC grades at varied concentrations on drug release and floating qualities were investigated. All of the prepared batches demonstrated good in vitro buoyancy.
CONCLUSION- The pills stayed buoyant for 12 hours. The optimal formulation (F8), consisting of HPMC K100M, was chosen based on in vitro drug release and phyco-chemical properties.

Index Terms **- Floating sustain release Tablets, Domperidone, Anti-emetics, Chemotherapy.**

INTRODUCTION

Emesis is the forced emptying of stomach and occasionally intestinal contents caused by activation of the vomiting centre in the medulla oblongata. An antiemetic is a medication that prevents vomiting and nausea. Antiemetic drugs are those that inhibit the effects of emetics. Antiemetics are often used to treat motion sickness as well as the adverse effects of opioid analgesics, general anesthetics, and cancer chemotherapy. They may be utilised for a variety of gastrointestinal conditions, particularly if the patient is dehydrated1.

DOMPERIDONE belongs to the Dopamine-2 receptor antagonist class and has a chemical formula of C22H24ClN5O2 with a molecular weight of 425.911g/mol. There is also a pale yellowish or virtually white powder. Domperidone dissolves in dimethyl formamide, methanol, ethanol, and 0.1N HCL but is almost insoluble in water. Domeperidone has a molecular weight of 425.9 g/mol, an XLogP3 of 3.9, and hydrogen bond donor, acceptor, and rotatable bond counts of 2, 3, and 5, respectively. Domperidone is absorbed orally and reaches peak blood concentration in 30 minutes; however, due to first-pass metabolism, bioavailability is only 15%. T1/2 is the plasma half-life, which is 7 hours. Domperidone binds to plasma protein in 91-93 percent of cases. The volume of distribution is 5.71 L/Kg, showing that the drug is dispersed broadly throughout the body. Domperidone is extensively metabolised in the liver, with the primary metabolic routes being N-dealkylation and hydroxylation catalysed by cytochrome P 450. Metabolites are inactive compounds. Domperidone metabolites are excreted in the urine.2-3

Domeperidone's ADME has Oral absorption is 93 percent, pre-systemic metabolism is 83-87 percent, volume of distribution is 5.71 L/kg, plasma protein binding is 91-93 percent, Tmax is 30 minutes, Cmax is 18.8ng/ml, and Pka is 7.9 milligrams per milliliter.

DOSAGE AND ADMINISTRATION 4-5

For upper GIT motility abnormalities, adults should take 10 mg orally three to four times per day, 15 to 30 minutes before meals, and at bedtime if necessary. Domperidone should be taken with caution in patients with hepatic impairment since it is highly metabolised in the liver (and in the elderly).

Knowledge of the drug's absorption mechanism from the Gastrointestinal (G.I.) tract, its general absorbability, the drug's molecular weight is 1000 Daltons, solubility at different pH is >0.1 mg/mL for pH 1 to pH 7.8, and visible partition coefficient is high are some physicochemical parameters for selecting a drug to be formulated in a sustained release dosage form. Similarly, some pharmacokinetic factors for drug selection include the estimation half-life of the drug. Total clearing is preferred between 2 and 8 hours. Bioavailability should not be dosage dependent, and absolute bioavailability should be at least 75%.

MATERIAL & METHODS

Shivalik Rasayan Ltd sent a complimentary sample of Domperidone (Bhiwadi, Rajasthan). Dow chemicals and J.R.S Pharma sent gift samples of hydroxypropyl methylcellulose (HPMC K4M, HPMC K15M, HPMC K100M), microcrystalline cellulose, and poly vinyl pyrollidone (PVP-K30). Peter Grevens & Evonik Pharma provided magnesium stearate and colloidal anhydrous silica (Aerosol). The rest of the solvents and reagents were of analytical quality. For the formulation, development, and optimization of the Floating Sustain Release Dosage form, the wet granulation method was used. Domperidone, HPMC K4M, HPMC K15M, HPMC K100M, and Microcrystalline cellulose (101) were shifted through a #40 sieve Binder was prepared according to the quantity of BOM (bill of materials) specified in Table 1. Water that has been cleansed RMG was used for wet granulation, and the resulting wet mass was co-sifted through an 8 mm screen. Wet granules were dried in an FBD until the desired LOD was attained, then sifted through sieve #20 and retails milled through a 1.5 mm screen. The lubricants mentioned in the BOM of Table -1 were used to lubricate the granules that had been manufactured. The blend was compacted into tablets with an average weight of 180 mg/tab using an 8.0mm standard concave punch with breakine on one side and plain on the other, and physiochemical characteristics were measured.

Table-1 Formulation Code of Domperidone

Sr. No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Domperidone	30	30	30	30	30	30	30	30	30
2	HPMC K4M	40	80	120	0	0	0	0	0	0
3	HPMC K15M	0	0	0	40	80	120	0	0	0
4	HPMC K100M	0	0	0	0	0	0	40	80	120
5	Microcrystalline Cellulose (PH 101)*	101.9	61.90	21.90	101.9	61.9	21.9	101.9	61.9	21.9
6	Povidone K-30	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4
7	Colloidal Anhydrous Silica	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
8	Magnesium Stearate	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Core weight		180	180	180	180	180	180	180	180	180

* Quantity (Inactive ingredient) to be compensation for assay correction of API.

In Vitro Buoyancy Studies: In vitro buoyancy was measured using the floating lag time, as described in a 1994 article by Jimenez-Castellanos et al (14). In a 100ml beaker, the pills were dissolved in 0.1 N HCl. The time it took the tablet to rise to the surface and float to the surface was used to compute the floating lag time.

Evaluation of Domperidone Tablet:

Parameters for Pre- and Post-Compression6:

Pre-compression parameters include the following: Physical parameters (appearance, diameter, thickness, weight variation, hardness, friability), content homogeneity, assay, and in-vitro drug release (dissolution) were assessed after compression for up to 12 hours.

Table.No.3 Parameters for Pre-compression of Domperidone batches F1 to F9

Formulation code	Derived Properties			Flow Properties		
	Bulk Density (g/ml)	Tapped Density (g/ml)	Loss on Drying	Angle of Repose (°)	Compressibility Index	Hausner's Ratio
F1	0.35±0.003	0.34±0.001	1.37±0.07	21.6±0.24	10.94±0.45	1.08±0.005
F2	0.32±0.004	0.44±0.002	1.29±0.12	29.6±0.11	25.00±1.48	1.34±0.016
F3	0.65±0.003	0.36±0.002	1.29±0.10	29.61±0.14	11.29±1.46	1.14±0.014
F4	0.25±0.004	0.42±0.006	1.47±0.11	29.59±0.35	14.99±2.24	1.46±0.002

F5	0.36±0.002	0.50±0.004	1.48±0.09	27.48±0.25	28.56±1.45	1.40±0.014
F6	0.34±0.003	0.44±0.005	1.35±0.11	25.79±0.14	14.11±1.88	1.11±0.022
F7	0.38±0.004	0.36±0.003	1.40±0.15	27.12±0.16	09.18±1.17	1.09±0.012
F8	0.36±0.003	0.50±0.002	1.20±0.12	28.32±0.12	26.76±1.14	1.36±0.014
F9	0.36±0.006	0.34±0.001	1.39±0.36	39±0.14	13.45±1.57	1.14±0.17

All Domperidone formulations have an angle of repose ranging from 27.81° to 32.71°, indicating that granule flow varies from excellent to good. Formulations F5, F7, and F8 had angles of repose ranging from 25° to 30°, suggesting that they have outstanding flow qualities, while the rest of the formulations had good flow properties. Powders with Carr's index (percent) values as high as 26 are considered to have acceptable flow properties. Powders with Carr's index (percent) values as high as 26 are deemed to have acceptable flow properties.6 The Carr's index for Domperidone formulations ranges from 20.87 percent to 26.78 percent, suggesting that the granules flow well to moderately well. The Parameters For Post compression:

improved formulation, F8, has a Carr's index of 26.76 percent. Aside from Carr's index, Hausner observed that the ratio DBmax/DBmin was related to inter particle friction, and he established that powders with low inter particle friction had ratios of approximately 1.35, indicating good flow. Aside from Carr's index, Hausner observed that the ratio DBmax/DBmin was related to inter particle friction, and he established that powders with low inter particle friction had ratios of approximately 1.35, indicating good flow. For all Domperidone formulations, the Hausner's ratio ranges from 1.25 to 1.35. F8, the improved formulation, has a Hausner's ratio of 1.350.01, indicating that it flows well.

Table No.4 Parameters for Post compression of Domperidone sustained release tablet.

Formulation code	Hardness (kg/cm^2)	Thickness (mm)	Weight variation (mg)	Friability (%)	Content uniformity (%)
					Domperidone
F1	8.5±0.05	3.6±0.04	180.1±1.9	0.5±0.02	98.65±0.32
F2	8.4±0.03	3.24±0.01	179.7±1.5	0.41±0.03	97.96±0.35
F3	8.8±0.04	3.14±0.01	185.0±1.6	0.4±0.04	98.49±0.62
F4	8.78±0.03	3.45±0.07	147.8±3.1	0.25±0.03	98.54±0.62
F5	8.45±0.01	3.4±0.02	189.1±1.9	0.51±0.01	98.47±0.30
F6	8.9±0.06	3.4±0.10	178.8±2.2	0.49±0.02	98.79±0.50
F7	9.45±0.08	3.64±0.13	179.5±3.4	0.36±0.03	97.95±0.89
F8	10.14±0.2	3.6±0.12	179.3±2.2	0.1±0.06	99.25±0.23
F9	10.12±0.1	3.4±0.11	181.1±1.2	0.2±0.04	98.25±0.24

All formulations are examined for hardness, friability, thickness, and weight fluctuation after compression. The hardness of all formed tablets is kept consistent at 10-12 kg/cm2. Because the amount of medicine varies between the layers, weight variation is a crucial measure to monitor. The thickness of the tablets varies between 3.5 and 3.8 millimeters and is within the standard variation. Another important factor that has a direct impact on the tablet's efficacy is its uniform distribution. Domperidone's content consistency ranges from 99.250.23 to 99.250.23.

Drug Release profile in all formulations:

Table No.5 Domperidone formulations F1 through F9 in vitro release profiles

S.No	Time (hrs)	Cumulative % of drug release								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	1	49.73	43.7	36.74	41.06	38.45	34.25	37.99	22.12	16.58
2	2	71.65	63.12	54.68	60.47	55.5	51.67	58.56	35.03	31.63
3	3	80.07	76.45	69.4	75.18	67.37	66.02	71.29	45.60	46.95
4	4	89.29	83.21	75.17	83.96	73.96	73.56	79.16	56.10	57.92
5	5	93.11	87.96	80.62	88.54	82.84	79.4	83.35	64.3	53.61
6	6	96.68	92.04	84.57	92.88	87.67	82.17	86.05	72.50	59.06
7	7	98.74	95.91	89.02	95.62	91.44	87.56	91.12	79.30	67.40
8	8	__	97.45	94.46	97.74	95.83	91.42	93.47	85.60	69.47

9	9	__	__	98.36	99.75	97.59	93.74	96.21	88.14	73.87
10	10	__	__	__	__	98.47	96.32	98.68	90.04	78.52
11	11	__	__	__	__	__	__	__	93.12	81.96
12	12	__	__	__	__	__	__	__	97.80	84.18
13	Infinity	__	__	__	__	__	__	__	98.92	__

As previously stated, several viscosity grades of sustain release polymers were utilised in the trials to investigate their impact on the dissolve release profile and to achieve the desired release profile for up to 12 hours. The sustain release polymers were utilised at three different dosage levels: 40 mg, 80 mg, and 120 mg, which are low, medium, and high, respectively.

In the instance of HPMC K4M, 40mg, 80mg, and 120mg of sustain release polymer were utilised to evaluate the influence on the dissolution release profile in F1, F2, and F3, respectively. The results demonstrate that in F1, the drug release profile at 1 hour was 49.73 percent, with a maximum drug release of 98.74 percent at 7 hours. The results demonstrate that the medication release profile at 1 hour in F2 is as follows:

43.7 percent, with a maximal drug release of 97.45 percent in 8 hours.

The drug release profile in F3 was determined to be 36.74 percent at 1 hour and 98.36 percent at 9 hours, according to the results.

In the instance of HPMC K15M, 40mg, 80mg, and 120mg of sustain release polymer were utilised to evaluate the influence on the dissolution release profile in F4, F5, and F6, respectively. The data demonstrate that in F4, the drug release profile at 1 hour was 41.06 percent, with a maximum drug release of 99.75 percent at 9 hours.

The results demonstrate that the medication release profile in F5 was determined to be 38.45 percent after 1 hour and 98.47 percent after 10 hours. The medication release profile in F6 was determined to be 34.25 percent at 1 hour and 96.32 percent after 10 hours, according to the results.

In the case of HPMC K100M, 40mg, 80mg, and 120mg of sustain release polymer were utilised to evaluate the influence on the dissolution release profile in F7, F8, and F9, respectively. The data demonstrate that in F7, the drug release profile at 1 hour was 37.99 percent, with a maximum drug release of 98.68 percent after 10 hours.

The medication release profile in F8 was determined to be 22.12 percent at 1 hour and 97.80 percent at 12 hours, according to the results. The drug release profile in F9 was determined to be 16.58 percent at 1 hour and 84.18 percent at 12 hours, according to the results.

Domperidone drug release should not be less than 85% at the end of the eighth hour, and the complete drug should be delivered within 12 hours. F8 was chosen as the best formulation since none of the other formulations met the above requirements. As a result, the above formulation has been refined and is now being tested for stability.

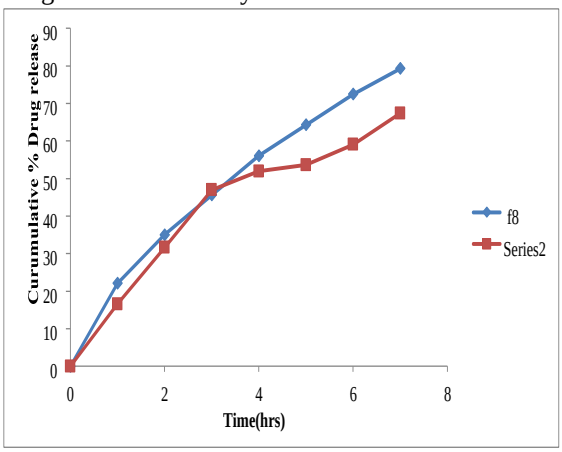

Fig No:1 Comparative invitro release data Domperidone F1 and F2 Formulation

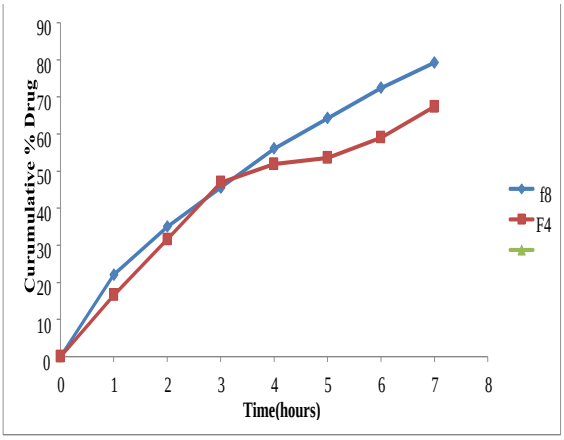

Fig No:2 Domperidone F3, F4, and F5 Formulation Comparative in vitro release data

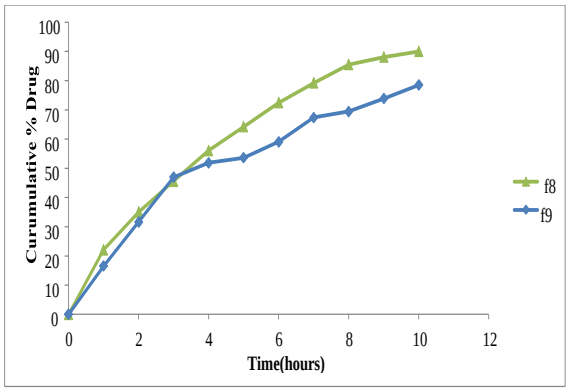

Fig No:3 Comparative invitro release data Domperidone F6 and F7 Formulation

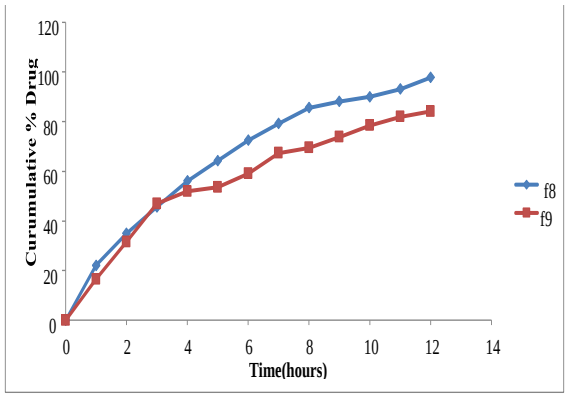

Fig No:4 Comparative invitro release data Domperidone F8 and F9 Formulation

RELEASE KINETICS

Table No.8 Kinetics of release data of different Domperidone batches

S.No	Batch No	First Order (R^2)	Korsmeyer Peppas (R^2)	Zero order (R^2)	Higuchi (R^2)	Hixson crowell (R^2)
1	F1	0.984	0.5888	0.7525	0.8616	0.8536
2	F2	0.9895	0.6097	0.8127	0.9078	0.8836
3	F3	0.8905	0.6355	0.881	0.4501	0.9094
4	F4	0.8821	0.6191	0.8148	0.909	0.9196
5	F5	0.9853	0.6408	0.9025	0.9675	0.9366
6	F6	0.9446	0.6447	0.8836	0.952	0.9118
7	F7	0.9888	0.5974	0.7859	0.9005	0.8991
8	F8	0.9442	07154	0.9411	0.9903	0.9856
9	F9	0.9689	0.686	0.8791	0.9505	0.9091

The release qualities of all formulations are examined. All of the formulations' kinetics are shown above. First order kinetics are followed by F1, F2, F5, F6, F7, and F9. whereas F3 is follow Hixson kinetics and F8 of the formulations followed Higuchi kinetics model. Finally, F8 formulation is optimized and follow Higuchi Kinetics model.

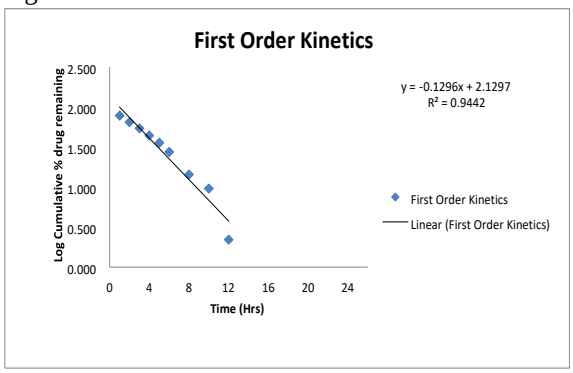

Fig No:5 Domperidone Optimized Formulation first order kinetics

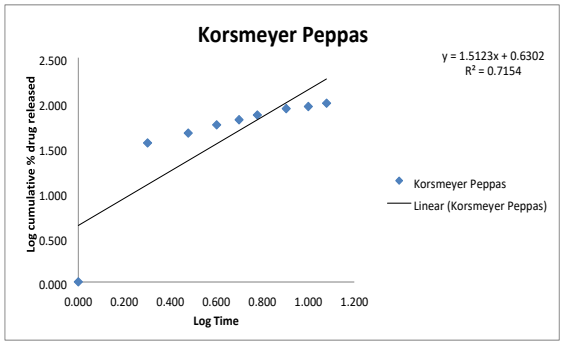

Fig No:6 Korsmeyer peppas for Domperidone Optimized Formulation

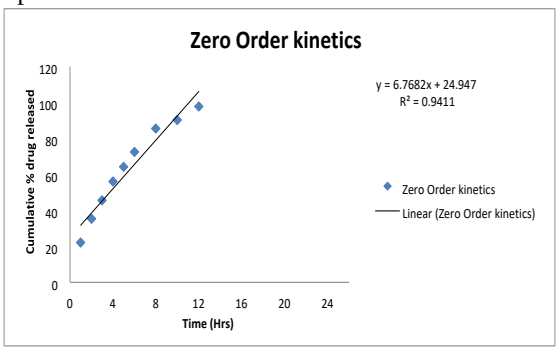

Fig No: 7 Domperidone Optimized Formulation Zero order kinetics

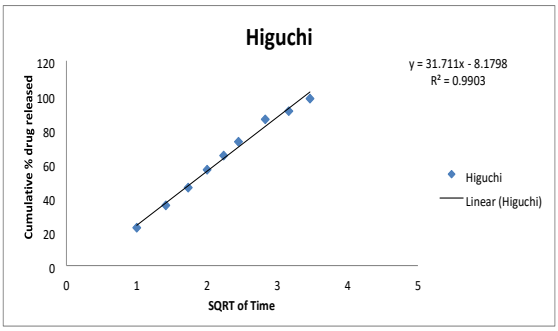

Fig No: 8 Higuchi kinetics for Domperidone Optimized Formulation

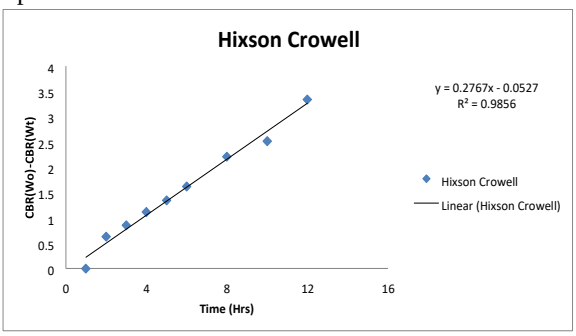

Fig No: 9 Hixson Crowell for Domperidone Optimized Formulation

Similarly, other pharmacokinetic characteristics for medication selection are drug estimated half-life, which should be between 2 and 8 hours, total clearance, which should not be dosage dependent, and absolute bioavailability of 75% or above.

CONCLUSION

In the presented study, an attempt was made "To Develop Domperidone Floating Sustained release tablet for the effective Treatment of Anti-Emetic therapy for chemotherapeutic patients". The Domperidone Floating sustained release tablet were prepared by using excipients (such as HPMC K100M, MCC 101, PVP K-30, Colloidal anhydrous silica and magnesium stearate) in different ratios. Different concentrations of polymer are used in the sustained release layer and their effect on the release of Domperidone is explored. The formulation F8 is found to be the best formulation since it meets the criteria in the drug release. The increasing drug release at the end of 12 hour is 98%.From the above data it is proof that the formulation F8 shows satisfactory sustained release in acidic media (0.1N HCl) and observed that it passes with all the Pharmacopoeial limits before and after the stability studies and is suitable composition for the Floating sustained release of Domperidone. Finally, it was concluded that F8 formulation shows the best release and stable in vigorous stability conditions and that may satisfy the objective of the study. The stability studies were performed according to in-house statement for the optimized formulation. The tablets were kept at accelerated condition (40±2^{o} C/ 75±5 % RH and 25±2^{o}C/60±5% RH) for a period of 3 months.

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