THE PHARMA RESEARCH

An International Journal of Pharmacy Research

Published on: 15-12-2013

ISSN: 0975-8216

IC Value: 4.54

Impact Factor: 0.591*

Formulation and Evaluation of Extended Release Tablets of Domperidone

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ABSTRACT

The main objective of the study is to develop reproducible formulation of extended release tablets of an antiemetic drug Domperidone. Different batches of matrix tablets were prepared by direct compression method. Before compression preformulation studies were done which includes characterization of blend and physical compatibility studies with excipients. Initially four trial batches were prepared by using four polymers; in-vitro drug release studies showed that batch having polyox and HPMC was found to be satisfactory. Five more batches were prepared for optimization of formulation. On the bases of drug release studies best optimized formulation was selected. Three batches of optimized formulation were prepared at different compression force to study its effects on drug release. The study shows that Domperidone tablets can be successfully formulated by direct compression technique by using hydrophilic polymer. The developed formulation can be considered as one of the promising extended release formulation.

Keywords: Polyox, HPMC, Extended release, Matrix tablets, Domperidone

INTRODUCTION

Over the past three decades, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of controlled drug delivery systems.

Oral solid dosage forms are the preferred route for many drugs and are still the most widely used formulations for new and existing modified release (MR) products. Over many years, MR technologies have been used to delay or extend the drug release in order to achieve the desired therapeutic benefits. The

drug release is extended over a number of hours, either by combining the drug with release retardant materials to form a matrix core, or by applying release modifying film coatings to cores containing the drug. Overall use of modified release technology aims to exert a spatial or temporal control on drug release from the dosage form.

Among different technologies used in controlled drug delivery, hydrophilic matrix systems are the most popular because of the simplicity of formulation, ease of manufacturing, low cost, FDA acceptance, and applicability to drugs with wide range of solubility (2, 3, and 4). Drug release from these systems is the consequence of controlled matrix hydration, followed by gel formation, textural or rheological behavior, matrix erosion, drug dissolution and diffusion, the significance of which depends on drug solubility, concentration and changes in matrix characteristics.

Hydroxypropylmethylcellulose (HPMC) is the most commonly used polymers in hydrophilic matrix formulations, owing to their solubility in water, availability in a wide range of molecular weight/viscosity grades, FDA acceptance, and unique swelling/erosion characteristics which can be utilized in modulating drug release profile.

MATERIALS AND METHODS:

Preparation of matrix tablets:

Tablets of Domperidone were prepared by direct compression method by 16 station compression machine-CMD 3-16 (manufactured by Cadmarch Machinary CO.Pvt.Ltd., India). Following steps were involved in tableting:

- All the ingredients were weighed accurately and sifted through BSS #36 and BSS #18.
- After sifting all the ingredients was blend together.
- Magnesium stearate was added in to the blend and blending was done for 5 minutes
- Then the final blends were compressed using 7mm round concave shaped punches.

Preparation of trial batches using different hydrophilic polymers:

Four separate batches were prepared using different amounts of hydrophilic polymers (HPMC5cps, MCC, Carbopol and Polyox 301). The formula of the blends with different amounts of hydrophilic polymers is given in Table 1.

Optimization of batches using Polyox 301 & HPMC (5 cps):

Five batches were prepared with ± amount of Polyox 301 & HPMC (5 cps). The formula of the blends is given in Table 2.

Preparation of optimized batch at different hardness:

Final optimized batch (F-8) was prepared at three different hardness (1-3kp, 3-5kp, 5-7kp); their release profiles were compared with the other batches.

Table 1: Formula of four trial batches (mg/tablet) with four different polymers

Ingredients	Quantity (mg/tablet)			
	F -1	F- 2	F- 3	F- 4
Domperidone	30	30	30	30
Avicel (PH102)	43.5	--	--	--
Carbopol	--	43.5	--	--
Polyox 301	--	--	--	43.5
HPC	--	--	43.5	--
HPMC 5CPS	43.5	43.5	43.5	43.5
PEG 6000	30	30	30	30
Silicon dioxide	1.5	1.5	1.5	1.5
Magnesium Stearate	1.5	1.5	1.5	1.5
Total weight	150	150	150	150

Table 2: Formula of optimized batches (mg/tablet) with Polyox 301

Ingredients	F-5	F-6	F-7	F-8	F-9
Domperidone	30	30	30	30	30
HPMC 5CPS	20	60	20	60	50
Polyox 301	60	20	60	20	30
PEG 6000	15	15	30	30	22.5
Lactose monohydrate	22	22	7	7	14.5
Silicon dioxide	1.5	1.5	1.5	1.5	1.5
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5
Total weight	150	150	150	150	150

PREFORMULATION STUDIES:

Determination of saturation solubility

The solubility of Domperidone in different media (water, 0.01N HCl, 0.1N HCl, 4.5 AB, 5.5 AB and pH 6.8 PB) is given in Table 3.

Table 3: Solubility of Domperidone in different media

Medium	Solubility of Domperidone (mg)/Medium(ml)	Category
Water	0.014mg/ml	Insoluble
0.01 N HCl	3.642mg/ml	Soluble
0.1N HCl	0.566mg/ml	Soluble
pH 4.5 Acetate buffer	0.608mg/ml	Soluble
pH 5.5 Acetate buffer	0.109mg/ml	Soluble
pH 6.8 Phosphate buffer	0.007mg/ml	Insoluble

The solubility values of Domperidone in 0.1N HCl, 0.01N HCl, pH4.5 comes under the soluble category i.e. (1 part of solute in 10-30 parts of solvent) and in pH6.8 PB solubility comes under the sparingly soluble category i.e. (1 part of solute in 30-100 parts of solvent).

Domperidone - excipients compatibility study:

FTIR spectra

Compatibility studies were performed using FTIR spectrophotometer. Characteristics absorption peaks of Domperidone were obtained at different wave number in different samples. Spectrum indicates that drug is compatible with formulation components.

Drug excipients compatibility study via physical evaluation

For the physical compatibility study the drug and the excipients were mixed together and kept for four weeks in various conditions and evaluated by physical evaluation.

Domperidone- Excipients compatibility study is reported in Table 4.

Characterization of pre-compressed blend of different formulation batches:

Results of characterization of the pre-compressed blend are given in Table 5. Following studies were done on blend:

- Bulk density
- Tapped density
- Carr's Index
- Hausner's Ratio
- Angle of Repose

Table 4: Drug -Excipient Physical compatibility study (Time-one month)

Sr.No	Name of the mix		State													
	Domperidone + Excipients	Ratio	Initial color	2-8^{0}C control				40^{0}C/75% RH				60^{0}C			
1	Domperidone		White powder	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
2	Domperidone + MCC (AVICEL PH 101)	1:10	White powder	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
3	Domperidone + Polyox 301	1:10	White powder	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
4	Domperidone + Hydroxy propylmethylcellulose (5 cps)	1:10	White powder	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
5	Domperidone + Carbopol	1:10	White powder	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
6	Domperidone + Magnesium stearate	1:2	White powder	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
7	Domperidone + Aerosil-200	1:2	White powder	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC

NC- No change in initial and final observation.
No physical incompatibility was found for the drug with selected excipients for the various batches.

Table 5: Evaluation of blends (F-1 to F-9)

Powder Blend	Angle of Repose (α)	Bulk Density	Tapped Density	Carr`s Index	Hausner`s Ratio
F-1	28.34(Good)	0.522	0.672	22.3(passable)	1.28(passable)
F-2	20.52(Excellent)	0.536	0.671	20.0(Good)	1.25(Fair)
F-3	19(Excellent)	0.574	0.746	23(Passable)	1.29(Passable)
F-4	23.56(Good)	0.538	0.673	20(Fair)	1.25(Fair)
F-5	20.1(Excellent)	0.548	0.678	19.1(Fair)	1.23(Fair)
F-6	25.2(Excellent)	0.527	0.667	20.9(Fair)	1.26 (Fair)
F-7	19.9(Excellent)	0.541	0.669	19.1(Fair)	1.23(Fair)
F-8	21.4(Excellent)	0.546	0.641	14.8(Good)	1.17(Good)
F-9	21.2(Excellent)	0.539	0.651	20.7(Fair)	1.20(Fair)

Among all the batches (F-1 to F-9) it was found that batch F-8 exhibited acceptable flow property with respect to angle of repose, Carr's index, Hausner's ratio.

EVALUATION OF TABLETS:

Hardness, Thickness, Friability, Average weight was performed for all the batches (F-1to F-9) and the data is presented in Table 6.

Table 6: Evaluation of tablets (F-1 to F-9)

Batches	Hardness (kPs)	Thickness (mm)	Friability (%)	Avg. wt. (mg)
F-1	8	4.35	0.03	149.12
F-2	6	3.70	0.03	150.17
F-3	4	4.25	0.03	150.33
F-4	3.99	3.99	0.02	150
F-5	2.5-3.5	4.01	0.02	152
F-6	3.5-4.5	4.04	0.03	151
F-7	2.5-3.5	4.18	0.03	151
F-8	3.5-4.5	4.17	0.03	150
F-9	3.5-4.5	4.01	0.02	152

Hardness, Thickness, Percentage friability and Average weight showed acceptable pharmacotechnical properties.

COMPARISON OF *in-vitro* DRUG RELEASE OF TRIAL BATCHES (F-1TO F-4)

The release profile of the four trial batches (F-1 to F-4) is mentioned in Table 7 and Figure 1.

Dissolution conditions:

Medium: 0.1 N HCl

Volume: 900ml

Apparatus: USP-II (Paddle)

RPM: 50 rpm

Time point: 1, 2, 3, 4, 6, 8, 10, 12, 16 hrs.

Temperature: 37°C ± 0.5°C

Volume of sample withdrawal: 10 mL

λ_{max} for absorbance : 284nm

Table 7: % Cumulative Drug release of four trial batches with four different polymers & optimized batches (F-5 TO F-9)

Time (hours)	% Cumulative Drug release								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
0	0	0	0	0	0	0	0	0	0
1	19.5	6.5	20.4	6.4	9.4	9.5	8.0	6.6	4.6
2	63.8	6.1	68.3	9.4	14.4	13.6	12.2	11.2	8.6
3	68.5	9.5	70.1	15.1	15.3	19.9	11.7	16.9	13.8
4	69.5	15.0	72.3	26.3	14.0	31.6	14.3	24.5	36.1
6	70.4	20.7	73.1	44.6	29.0	59.6	25.5	45.1	57.6
8	72.8	28.3	78.3	63.9	43.4	90.6	59.3	75.3	80.2
12	NA	31.3	NA	80.6	53.8	100.6	64.6	92.1	92.0
16	NA	37.5	NA	80.1	70.6	101.5	76.8	100.8	93.3
17	NA	45.2	NA	82.3	91.8	101.1	91.4	100.1	97.4

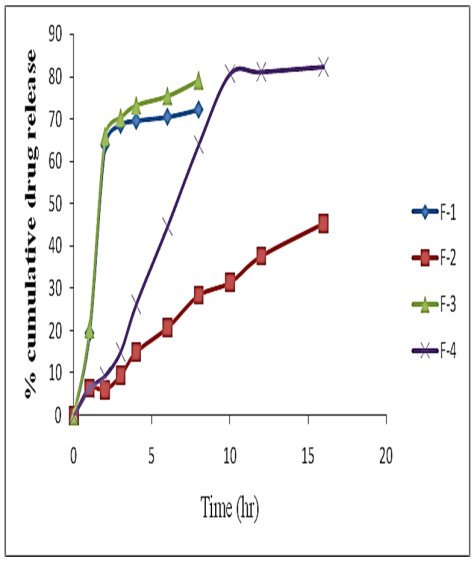

Figure 1: Comparative release profile of four trial batches (F-1, F-2, F-3 and F-4)

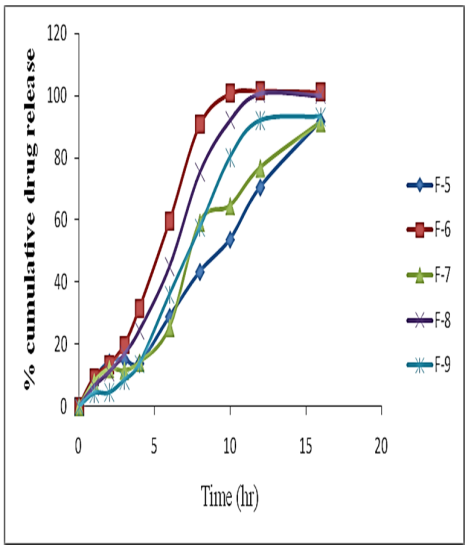

Figure 2: Comparative release profile of optimized batches

By comparing the % cumulative drug release of the four batches with product it was found that Batch F-4 demonstrated a controlled release as compared to other batches & selected for comparision.

The release profile of the five optimized batches (F-5 to F-9) is mentioned in Table 8 and Figure 2.

EFFECT OF HARDNESS ON % CUMULATIVE DRUG RELEASE (F-10 – F-12):

Effect of hardness on the final optimized Batch made with Polyox 301: HPMC (5cps) is mentioned in Table 9 and Figure 3.

Table 9: Effect of hardness on % cumulative drug release on the final batch

Time (hours)	Effect of hardness on %cumulative drug release		
	F-10 (1-3 kp)	F-11 (3-5 kp)	F-12 (5-7 kp)
0	0	0	0
1	7.2	6.6	5.2
2	12.5	11.2	9.8
4	17.1	16.9	15.1
6	24.7	24.5	22.1
8	47.2	45.1	41.5
12	73.2	75.3	74.2
16	95.1	92.1	90.2
20	100.4	100.8	97.5
24	100.2	100.1	98.5

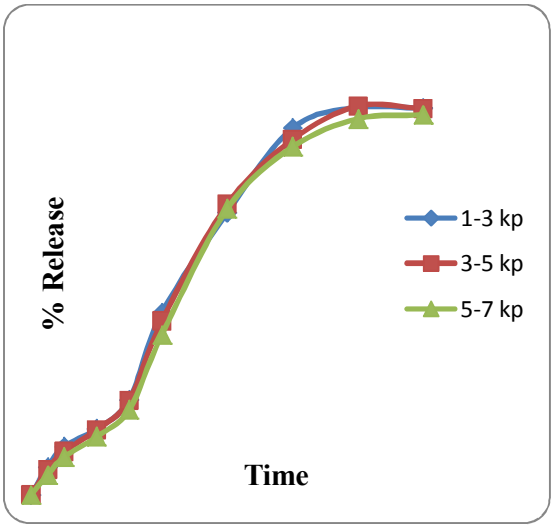

Figure 3: Effect of hardness on %cumulative drug release

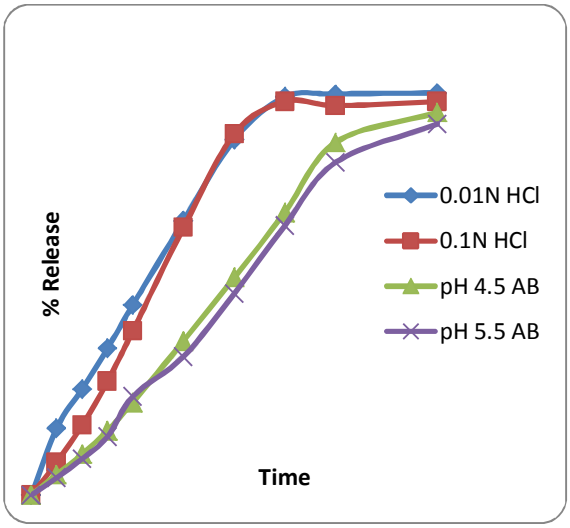

Figure 4: Comparative release profile of final formulation in different media

MULTIMEDIA DISSOLUTION STUDIES OF OPTIMIZED BATCH:

Table 10: Multimedia dissolution studies of final batch

Time(hr)	0.01N HCl	0.1N HCl	pH 4.5 AB	pH 5.5 AB
0	0	0	0	0
1	17.4	8.5	5.3	4.5
2	27.5	18.1	10.6	9.4
3	38.0	29.5	16.7	15.1
4	49.3	42.6	24.0	25.6
6	71.1	69.4	40.0	35.9
8	92.1	93.6	57.4	52.3
10	103.2	102.0	73.3	69.9
12.	103.9	100.9	91.4	86.2
16.	104.2	101.9	99.1	96.2

SUMMARY AND CONCLUSION:

The main objective of this study is to develop reproducible formulations of extended release tablet of an antiemetic drug Domperidone. The outcome of the study conducted are following:

1) λmax = 284 nm was found to be absorption maxima of drug Domperidone in water, 0.01 N HCl, 0.1N HCl, pH 4.5 AB, pH 5.5 AB and pH 6.8 PB.
2) In the saturation solubility study it was found that the drug Domperidone is more soluble at acidic pH.
3) The physical compatibility study at 2-8° C, 40º C and 40º C/75% RH showed that Domperidone and excipients used found to be physically compatible.
4) Characterization of blend like Bulk density, Tapped density and Angle of repose was done and Carr's index and

Hausner's ratio was calculated and found to be satisfactory.

5) Four polymers used in polymer selection batches, the ratio of polyox and HPMC was found to be satisfactory.
6) The dissolution study of various batches showed that:
   - In F-1 the formulation failed may be due to disintegration of tablet with in 8 hrs.
   - In F-2 the formulation failed because it released only 45 % in 16 hrs.
   - In F-3 the formulation failed may be due to disintegration of tablet with in 8 hrs.
   - In F-4 the formulation gives the desired result. Hence this formulation was selected for further optimization study.
7) The optimization formulations were studied for *in-vitro* drug release study among them batch F-8 showed that the formulation released drug for 12 hrs in a sustained manner.
8) Three batches of F-8 were prepared and *in-vitro* release studies were done. Thus validated the reproducibility of the formulation.
9) Three batches were prepared at different compressional force. It was found that 3-5 Kp is optimum hardness to formulate the Domperidone tablets. These tablets also had acceptable friability.
10) The study shows that Domperidone tablet can be successfully formulated by direct compression technique by using hydrophilic polymer .The developed formulation should be considered as one of the promising extended release formulation.

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