FORMULATION AND *IN-VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF DOMPERIDONE

Chhitij Thapa,[1] Roma Chaudhary[1]

ABSTRACT

INTRODUCTION

Domperidone is a unique compound with gastro kinetic and antiemetic effects. It is used in the management of disorder by impaired motility like gastroesophageal reflux (in some instances), gastroparesis, dyspepsia, heartburn, epigastric pain, nausea, vomiting, and colonic inertia. The sustained release system is a widely accepted approach for slow drug release over an extended period to address the challenges of conventional oral delivery, including dosing frequency, drug safety, and efficacy. The study aims to formulate a domperidone sustained release tablet and compare the dissolution rate with the marketed formulations.

MATERIAL AND METHODS

Sustained release matrix tablets of domperidone were prepared by wet granulation method using different polymers such as HPMC K4M, ethyl cellulose, *Gum acacia*. Pre-compression studies like angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio, and post-compression studies like weight variation, thickness, hardness, friability, drug content, and *in-vitro* drug release were evaluated.

RESULTS

The release profile of domperidone sustained-release tablets was studied spectrophotometrically. The *in-vitro* dissolution study suggests the minimum %-cumulative drug release with 98.33% in F5. The %-cumulative drug release was maximum in F3 with 99.69%. The *in-vitro* drug release of all the formulations was non-significant compared to the marketed formulation ($p<0.05$), exhibiting the sustained-release property by all the formulations.

CONCLUSION

The pre-compression study concludes the better flow property of the granules of different formulations. The sustained release domperidone tablets were prepared successfully by the wet granulation method. The post-compression parameters of different formulations were within the acceptable range.

KEYWORDS Domperidone, Sustained release tablet, Wet granulation method.

1. Department of Pharmacy, Universal College of Medical Sciences, Bhairahawa, Nepal

DOI: http//doi.org/10.3126/jucms.v8i02.34286

For Correspondence
Chhitij Thapa
College of Pharmacy
Universal College of Medical Sciences
Bhairahawa, Nepal
E:mail: kshitizthapa07@gmail.com

INTRODUCTION

The oral route is known as the widely accepted route because of convenience in self-administration, compactness, and easy manufacturing.[1] Among the available oral dosage forms, a tablet is the most popular with better ease of use and low cost of production, high stability, the possibility of masking objectionable odor and bitter taste, precise dosing, and ease of administration.[2] The oral-conventional formulation provides a timely release of the drug to maintain the drug concentration in the therapeutically effective range. However, it is necessary to take several times a day.[3]

Sustained release drug delivery systems solve the problems related to the conventional delivery system.[4] They help in maintaining the optimal concentration of drugs having a narrow therapeutic range and short half-life and also profoundly used to prolong the effect of drugs, decrease the frequency and enhance patient compliance and clinical efficacy. The plasma drug level is achieved by an immediate release of the initial dose and sustained by a maintenance dose of sustained-release matrix tablets for a predetermined time.[5] However, there is a probability of dose dumping and first-pass metabolism. Moreover, there is a need for education for proper medication also.[8] The dissolution of a drug from sustained-release formulation includes the formation of a gel layer around the tablet surface because of hydrophilic or hydrophobic polymer hydration when immersed in a G.I. fluid resulting in the swelling and increase in size followed by dissolving or eroding of the matrix allowing drug release. While the soluble portion of the drug is released by diffusion through the gel layer, the insoluble part release by tablet erosion.[8]

Domperidone is a potent drug exerting its gastro kinetic action on the peripheral dopamine sub-2 receptors in the GIT with both gastro kinetic and antiemetic effects. There is an interest in anti-dopaminergic prokinetic agents after the withdrawal of cisapride, a 5-HT4 agonist.[6] Clinically domperidone is useful in the management of disorder characterized by impaired motility, like gastroesophageal reflux, gastroparesis, dyspepsia, heartburn, epigastric pain, nausea, vomiting, and colonic inertia.[5] Domperidone tablet can be given up to thrice a day with a maximum dose of 30 mg per day. Formulation of sustained release tablet aims to minimize the frequency of drug administration and obtain a better therapeutic response.[7]

MATERIAL AND METHODS

Universal Formulations Pvt. Ltd., Rupandehi, Nepal provided domperidone. HPMC K4M, and ethyl cellulose were purchased from kemphasol. *Gum acacia*, PVP K30, magnesium stearate, mannitol were available in the college laboratory. All the chemicals used were of analytical grade.

Formulation of sustained-release tablets of domperidone

Sustained-release tablets of domperidone were formulated by the wet granulation method. Domperidone and the excipients were preliminarily sieved, mixed in geometrical ratio. The binder solution (PVP K30) was prepared by the addition of water during formulation. The binder solution was added at a controlled rate to the powder mixture with uniform mixing to achieve a wet mass and then sieved to achieve wet granules. The wet granules were dried in a tray dryer at 60° C for one hour. The dried granules were then sieved and lubricated with magnesium stearate by uniform mixing.[5]

Table 1. Formulation design of domperidone sustained-release tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Domperidone	20	20	20	20	20	20	20	20	20
HPMCK4M	120	150	180	-	-	-	-	-	-
Ethyl cellulose	-	-	-	120	150	180	-	-	-
Gum acacia	_	_	_				120	150	180
PVPK30	9	9	9	9	9	9	9	9	9
Magnesium stearate	6	6	6	6	6	6	6	6	6
Mannitol	145	115	85	145	115	85	145	115	85
Total	300	300	300	300	300	300	300	300	300

Evaluation of tablets

Pre-compression parameters

Bulk Density

Bulk density was determined by adding 3 gm of dry granules into 10 ml graduated measuring cylinder, and bulk volume was noted down. For the determination of bulk density, a ratio of weight to the bulk volume of the granules was calculated.[9]

$$\text{Bulk density} = \frac{\text{weight of the powder}}{\text{bulk volume of the powder}}$$

Tapped density

Tapped density was determined by adding 3 gm of dry granules into a 10 ml graduated measuring cylinder and then tapped to 100 tapings on the hard plane surface up to 2 cm height until the change in the volume approached constant value. Tapped density was determined as a ratio of weight to the tapped volume of the granules.[9]

$$\text{Tapped density} = \frac{\text{weight of the powder}}{\text{tapped volume of the powder}}$$

Tapped density= weight of the powder/ tapped volume of the powder

Carr's Index
Compressibility is an indication of ease, with which a material can be induced to flow.[10] Carr's index of the powder was determined as:

$$\text{Carr's index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100$$

Hausner's ratio
Hausner's ratio is related to inter particular friction, which could predict powder flow properties.[11] Hausner's ratio of the powder was determined as:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{bulk density}}$$

Hausner's ratio values less than 1.25 indicates a good, while greater than 1.25 indicates a poor flow.

Angle of repose
The angle of repose was determined by the fixed funnel method.[12] Accurately weighed quantity of samples were taken in a funnel. The height of the funnel was adjusted in such that the tip of the funnel just touches the apex of the heap of the samples taken. The samples were passed through the funnel freely onto the surface. The height and diameter of the powder conical pile were measured, and the angle of repose calculated using the following equation.

$$\text{Tan } \theta = \frac{h}{r}$$

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

Post-compression parameters
Appearance
Tablets were evaluated for appearance, cracks, depression, and pinholes.

Weight variation
The weight of the tablets was determined to ensure the proper amount of drug in the tablet formulation.[13] The weight variation test was conducted by weighing 20 tablets individually and calculating the average weights. The weight variation of the tablet was calculated as:

$$\text{Weight variation} = \frac{\text{individual weight} - \text{average weight}}{\text{average weight}} \times 100$$

Tablet hardness
The hardness of each batch of the tablet was checked by using Monsanto hardness tester in terms of kg/cm. Ten tablets were chosen randomly and tested for hardness. The average hardness of ten tablets was recorded.[14]

Friability
Friability testing of the formulations was conducted in the Roche friabilator. Twenty different tablets were weighed, recorded and placed in the Roche friability testing apparatus, rotated at the speed of 25 rpm for 100 revolutions. After the complete revolution tablets were removed, dedusted and again weighed and recorded. The permitted friability limit is less than one percent.[15] The percent friability was determined using the following formula:

$$\text{Friability} = \frac{W1 - W2}{W1} \times 100$$

Where W1= initial weight of the table
W2= final weight of the tablet.

Dimensions
Dimensions of tablets like the thickness and diameter were measured by a digital Vernier caliper, and these values were checked to adjust the punch position at the initial stages of compression.[16]

Assay (drug content)
Ten tablets from each formulation were taken and powdered. The powder equal to 20 mg drug was weighed and dissolved in a 100 ml volumetric flask using methanol as a solvent and filtered. Ten ml of filtered solution was transferred to a 100 ml volumetric flask, and the volume adjusted.[13] The absorbance of the diluted solution was determined spectrophotometrically at 284 nm against methanol as blank.[14] The assay percent of domperidone was calculated as:

$$\text{Content per tablet} = \frac{\text{absorbance of sample}}{\text{weight taken}} \times \frac{\text{Dilution factor}}{E1\%, 1cm} \times \frac{\text{Average weight}}{100}$$

Where,

$$E1\%, 1cm = \frac{\text{Absorbance of standard}}{\text{weight taken}} \times \frac{\text{Dilution factor}}{\%\text{ purity}}$$

Similarly, the assay was calculated as:

$$\text{Assay} = \frac{\text{content per tablet}}{\text{claim per tablet}} \times 100$$

***In-vitro* drug release study**
In-vitro drug dissolution test was carried out in 0.1 N HCl for the first two hours and into the phosphate buffer medium (pH 6.8), up to 24 hours using USP Type II dissolution test apparatus. The rotation of the paddle was fixed at 100 rpm and the temperature set at 37 ±0.5˚C. The five ml sample was withdrawn, filtered, and diluted to 50 ml with a dissolution medium. The absorbance of the sample solution was measured

spectrophotometrically at 284 nm.[15] The *in-vitro* drug release of the formulations was compared with domperidone sustained-release tablets.

Statistical analysis
All the experiments were run in triplicate, and results expressed as mean ±SD. Graph pad prism version 7 software (Graph pad software Inc., La Jolla, CA) was used for the statistical analysis, and the data analyzed by Tukey's post hoc multiple comparison test: statistical significance was predefined at $p<0.05$.

RESULTS AND DISCUSSION

Angle of repose
The angle of repose study suggested the minimum value with 29.03 ±0.6° in F1 and maximum in F8 with 34.30 ±0.5°. Study suggests a good flow property of all formulation.

Bulk and tapped density
The study suggests the minimum bulk density with 0.50 ±0.02 gm/ml in F1 and maximum bulk density with 0.55 ±0.2 gm/ml in F6. Similarly, the observed tapped density was higher in F5 with 0.61 ±0.4 gm/ml and lower in F2 with 0.57 ±0.2 gm/ml.

Carr's index
Carr's index study suggests the minimum value with 11.56 ±0.4 in F2 exhibiting good compressibility and maximum in F7 with 16.50 ±0.4 indicating fair compressibility.

Hausner's ratio
The study on Hausner's ratio suggests the minimum Hausner's ratio with 1.11 ±0.03 in F2, which is a good flow. Similarly, The F4 with 1.19 ±0.01 shown the maximum Hausner's ratio with a fair flow property. The result of the Hausner's ratio of different formulation powder is in Table 2.

Table 2. Result depicting the pre-compression parameter of the powder

Batch code	Angle of repose (?)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Hausner's ratio
F1	29.03 ±0.6	0.50 ±0.02	0.57 ±0.3	12.37 ±0.5	1.14 ±0.02
F2	30.36 ±0.7	0.51 ±0.01	0.57 ±0.2	11.56 ±0.4	1.11 ±0.03
F3	29.90 ±0.8	0.52 ±0.01	0.59 ±0.3	12.44 ±0.5	1.13 ±0.02
F4	30.77 ±0.8	0.51 ±0.4	0.61 ±0.2	15.10 ±0.4	1.19 ±0.01
F5	30.11 ±0.9	0.53 ±0.3	0.61 ±0.4	14.01 ±0.5	1.15 ±0.01
F6	29.51 ±0.8	0.55 ±0.2	0.64 ±0.3	14.24 ±0.2	1.16 ±0.04
F7	34.20 ±0.9	0.50 ±0.3	0.59 ±0.2	16.50 ±0.4	1.18 ±0.02
F8	34.30 ±0.5	0.51 ±0.5	0.60 ±0.3	16.15 ±0.5	1.17 ±0.02
F9	33.5 ±0.7	0.51 ±0.3	0.60 ±0.3	15.35 ±0.5	1.17 ±0.03

Weight variation and thickness
The result of the weight variation suggests a minimum average weight with 299.6 ±1.18 mg in F8 and a maximum average weight with 301.3 ±2.55 mg in F4 formulation. The result satisfies the pharmacopeia requirement. The study suggests the minimum thickness with 5.24 ±0.01 mm in F1 and maximum in F7 with 5.31 ±0.01 mm.

Hardness and friability
The minimum hardness with 7.20 ±0.11 kg/cm^2 was found in F5 formulation, and maximum in F3 with 10.20 ±0.19 kg/cm^2. Friability was minimum with 0.29% in F3, and maximum in F9 with 0.44 %.

Drug content (Assay)
The minimum drug content with 97.8% was observed in F8 formulation and maximum in F1 with 100.6%. The drug content of all the formulations was within the pharmacopeia range. The result of the drug content is in Table 3.

Table 3. Result depicting the post-compression parameter of the tablet

Batch code	Mean weight (mg) ±SD, n=20	Mean thickness (Kg/cm²) ±SD, n=6	Hardness (Kg/cm²) ±SD, n=10	Friability (%), n=20	Drug content (mg%) ±SD, n=10
F1	299.9 ±1.51	5.24±0.01	7.50±0.10	0.42	100.6 ±0.05
F2	300.55 ±2.30	5.26 ±0.03	9.40 ±0.08	0.4	99.5 ±0.1
F3	300.15 ±1.66	5.27 ±0.07	10.20 ±0.19	0.29	99.05 ±0.16
F4	301.3 ±2.55	5.24 ±0.07	7.60 ±0.12	0.36	98.49 ±0.19
F5	300.25 ±1.48	5.24 ±0.07	7.20 ±0.11	0.4	98.29 ±0.14
F6	300.2 ±1.43	5.24 ±0.02	9.20 ±0.13	0.33	98.11 ±0.66
F7	300.65 ±1.53	5.31 ±0.01	9.70 ±0.15	0.34	98.6 ±0.45
F8	299.6 ±1.18	5.28 ±0.02	8.40 ±0.04	0.33	97.8 ±0.82
F9	300.6 ±1.30	5.28 ±0.01	7.70 ±0.10	0.44	98.95 ±0.38

***In-vitro* drug release study**
The *in-vitro* drug release suggests a minimum percentage cumulative drug release with 98.33% in F5, and maximum in F3 with 99.69%. The result of the *in-vitro* drug release is in figure 1. The release of all formulations was non-significant compared to domperidone marketed sustained release formulation ($p<0.05$), exhibiting the sustained release properties of the formulations.

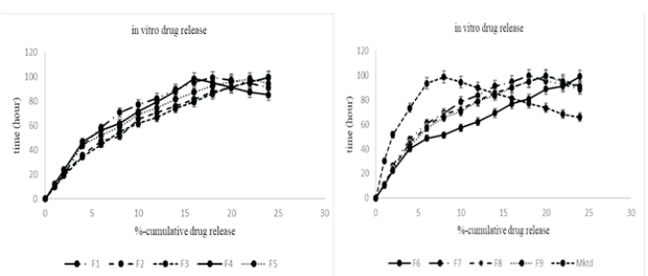

Figure 1. Cumulative *in vitro* drug release profile of different formulations

DISCUSSION

The study on the flow suggests a good flow property of the powder particles. The angle of repose of all formulations was within the acceptable range owing to the roughly spherical shape of the powdered particles.

The study on the bulk density, tapped density, Hausner's ratio,

and the Carr's index suggests minimum value within the acceptable range, indicating minimal density difference before and after tapping of the powder and better compressible characteristics.

The weight variation and the thickness were within the acceptable range, indicating uniform fill volume of the powder particles during the compression stage, and uniform mixing between the powder ingredients during the granulation phase.

The hardness and friability of all the formulations were acceptable, indicating the adequate mechanical strength to withstand the external shock experienced during the time of processing and shipping of the tablets.

During the granulation stage, no significant segregation between the ingredient of the powder was observed, and the complete mixing was assured by mixing by doubling up technique, consequently, the drug content in all the formulations was observed within the acceptable pharmacopeia limit.

All the formulations exhibited better-sustained release property. However, the cumulative %-drug release of the formulations (except F2, F3, and F6) decreased after reaching the maximum value, which may be due to complete drug release and addition of the fresh dissolution medium in each sampling to maintain the sink condition. A formulation comprising HPMC K4M instead ethyl cellulose as a binder exhibited better-controlled release as reported previously by Ojoe et al.[19] Gum acacia as a binder exhibited an intermediate binding effect with some drawbacks. The uncontrolled rate of hydration, microbial contamination, reduced viscosity on storage, pH-dependent solubility, and batch-to-batch variation are the drawbacks of the natural gums.[17,18]

CONCLUSION

Sustained-release tablets of domperidone were successfully prepared by the wet granulation method. Formulation (F3) exhibited better sustain release up to 24 hours with percentage cumulative drug release up to 99.69%. The pre-formulation and post-formulation study also suggests better results in F3 formulation among all nine different formulations. The method of analysis for domperidone was simple and rapid. The *in-vitro* drug release profiles of all formulations exhibited sufficient sustained released properties of the drug.

DECLARATION OF INTEREST

None

ACKNOWLEDGMENT

We are thankful to Universal formulations (Rupandehi, Nepal) for providing the sample drug domperidone. Sincere acknowledgment goes to Professor Dr. Ananda Kumar, The Principal, Universal college of Medical Sciences (Siddhartha Nagar, Nepal) for his valuable support to make this research possible. Thanks to the Universal College of Medical Sciences (Siddhartha Nagar, Nepal) for allocating necessary laboratory premises for the successful conduction of this work.

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