Formulation and Evaluation of Orodispersible Tablet of Domperidone

Ashiqul Islam, Syed Shabbir Haider and Md. Selim Reza

Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh

ABSTRACT: The aim of the present study was to develop and evaluate orodispersible tablets of domperidone by direct compression method. Sodium starch glycolate (SCG), Kollidone CLSF and sodium bicarbonate were used as disintegrants to achieve the desired disintegration time required for orodispersible tablets. To mask the bitter taste of drug, impart sweetness and to offer a better feeling in mouth, saccharin sodium, aspartame, citric acid, menthol and lemon flavor were also added. Mannitol and lactose were used as sugar based multifunctional diluents. The prepared tablets were evaluated for their physical (hardness, friability, weight variation), organoleptic (taste, mouth-feel, color) and functional (disintegration time) properties and for the drug content. The excipients were used in various concentrations in order to optimize the desired properties. SCG and Kollidone CLSF, used in 5.5% and 4% respectively, gave satisfactory disintegration time using BP instrument and within the mouth. Combination of saccharin sodium (1.5%) and aspartame (3%) along with mannitol (40%) and other excipients effectively masked the bitterness and provided satisfactory sweetness level. Incorporation of 0.05% menthol provided excellent mouth feeling as assessed by a panel of volunteers. Hardness and friability values were also optimized in the formulations to produce tablets of acceptable physical stability and mechanical strength. Weight variation and drug content of all formulations fully complied with the official specifications.

Key words: Domperidone, orodispersible tablets, mouth dissolving tablets, super disintegrants, sodium starch glycolate, Kollidone CLSF, taste masking.

INTRODUCTION

Although oral tablet is the most widely used dosage form, patients often experience difficulty in swallowing conventional tablets when water is not available nearby. Pediatric and geriatric patients may also encounter inconvenience in swallowing tablets even when taken with water.[1] Orodispersible tablets (ORDs), also known as 'mouth dissolving tablets', offer the advantage of both liquid and conventional tablet formulations allowing the ease of swallowing the drug in the form of liquid dosage form. ORDs rapidly disintegrate in the mouth with the help of saliva to form a dispersion which can be swallowed easily without the need of taking water.[1,2] Other advantages of ODTs that have been investigated are their potential to increase the bioavailability of poorly water soluble drugs through enhancing the dissolution profiles. Target patient groups also include institutionalized psychiatric patients as well as hospitalized or bed-ridden patients suffering from a variety of ailments such as stroke, thyroid disorders, Parkinson's disease, and other neurological problems such as multiple sclerosis and cerebral palsy.[3]

The fast-dissolving property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to developing ODTs involve maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation.[4] Various methods have been reported for the preparation of ODTs which include tablet molding, spray drying, sublimation, lyophilization, solid dispersion, addition of disintegrants etc.[1-4,7-10] Each method has its own advantages and limitations.

Correspondence to: Md. Selim Reza
Tel: +880-2-9661920-73 Extn. 8182; Fax: +880-2-8615583
Email: selim.du@gmail.com

Domperidone (Figure 1), 5-chloro-1-[1-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)propyl] piperidin-4-yl]-1,3-dihydro-2H-benzimidazol-2-one, is an antidopaminergic drug and used generally to suppress nausea and vomiting or as a prokinetic agent. It has also been used to stimulate lactation.[5,6] It is white or almost white powder, practically insoluble in water but soluble in dimethylformamide, slightly soluble in alcohol and in methanol.[6] In the present study, domperidone was selected as a model compound to develop an acceptable ODT formulation of this drug. The method of direct compression was employed for the product in order to eliminate the limitations of previously described methods.[4] Various formulation and processing variables were investigated to achieve the desired purpose and the prepared domperidone orodispersible tablets were evaluated by standard quality control methods.

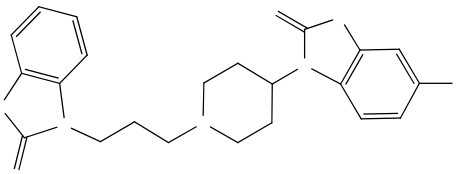


Figure 1. Structure of domperidone

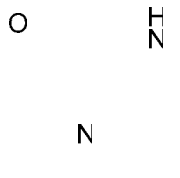
MATERIALS AND METHODS

Materials. Domperidone B.P. (assay 99.4%) and menthol were obtained from China National Native Produce Ltd. Sodium starch glycolate (SCG), sodium bicarbonate, saccharin sodium and maize starch were purchased from Chunghwa Chemical Synthesis & Biotech Co. Ltd., Taiwan. Kollidone CLSF and starch 1500 were obtained from Colorcon Asia Pvt. Ltd., USA. Aspartame and mannitol were obtained from The Nutrasweet Company, USA. Citric acid and magnesium stearate were locally purchased from Remo Chemical Ltd., Bangladesh. Microcrystalline cellulose and (Avicel 102) and lactose were supplied by Mingtai Chemical Ltd., Taiwan. Colloidal Silicon Dioxide (Aerosil 200) was procured from Cabot, Germany. Green lake color and lemon flavor were products of BASF, Germany and IFF Ltd., UK respectively. The above materials were of pharmaceutical grade and all other reagents were of analytical grade.

Apparatus. UV-VIS Spectrophotometer (Uvmini-1240, Shimadzu Corporation, Japan), Sartorius Electronic Balance (Germany), Erweka Friability Tester (Germany), Dr. Schleuniger Pharmatron Tablet Tester (Model 6D, USA).

Formulations of domperidone orodispersible tablets. After some preliminary trials and screening, five formulations were finally employed for detailed study (Table 1).

Preparations of domperidone ODT. The orodispersible tablets were prepared by direct compression method according to formula given in Table 1. A total number of five formulations were prepared, each formulation batch comprising of 1000 tablets. For formulation F1, the required amount of domperidone, SSG, maize starch, Kollidon CLSF, saccharin sodium, aspartame, starch 1500, mannitol, lactose and Avicel 102 were taken in a stainless steel bowl and mixed thoroughly for 15 minutes. Then citric acid and sodium bicarbonate were added and mixed for 10 minutes. Then lemon powder flavor and Green lake color were added sequentially and mixed for 5 minutes. Finally, lubrication was performed by adding Aerosil and magnesium stearate, and mixing for additional 5 minutes. The dry mixture was compressed into tablets with a Manesty 16 station tablet press (England) using round and flat faced D-type tablet tooling (diameter 9.5 mm). For other formulations, the order of mixing was altered. In cases of formulation F2, F3 and F4, the drug, Avicel 102, lactose and maize starch were mixed thoroughly in a stainless steel bowl for 10 minutes. Then, SSG and Green lake color were taken and mixed with the previous ingredients for 10 minutes. After that, saccharin sodium, aspartame, starch 1500 and mannitol were added to the mixture and mixed for 15 minutes. Next, citric acid, sodium bicarbonate, Kollidon CLSF and lemon powder flavor were added and mixed for 15 minutes. Lastly lubrication was performed by blending Aerosil and magnesium stearate with the previous mixture for 5 minutes. The



preparation of formulation F5 was quite similar to those of F2 to F4 except that a small amount of menthol was added additionally during the mixing of saccharin sodium, aspartame, starch 1500 and mannitol. The final dry mixture was compressed into tablets following the same manner as previously mentioned for formulation F1.

Table 1. Formulations of domperidone orodispersible tablets

Ingredient (mg / tablet)	Formulation code				
	F1	F2	F3	F4	F5
Domperidone BP	10.0	10.0	10.0	10.0	10.0
Sodium Starch Glycolate (SSG)	12.0	12.0	15.75	19.25	19.25
Kollidone CLSF	8.0	8.0	10.5	14.0	14.0
Saccharin Sodium	0.5	3.0	5.25	5.25	5.25
Aspartame	7.0	7.0	8.75	10.5	10.5
Citric acid	1.0	1.0	1.75	2.45	2.45
Sodium Bicarbonate	4.0	4.0	5.25	7.0	7.0
Lactose	8.0	30.0	35.0	35.0	35.0
Maize Starch	4.0	30.0	35.0	35.0	35.0
Flavor (Lemon)	2.0	3.0	3.5	3.5	3.5
Color (Green lake)	0.2	0.3	0.35	0.35	0.35
Aerosil 200	2.0	3.0	3.5	3.5	3.5
Magnesium Stearate	1.0	1.5	1.75	1.75	1.75
Mannitol	100.0	120.0	140.0	140.0	140.0
Starch 1500	20.0	20.0	20.0	20.0	20.0.
Menthol	-	-	-	-	0.175
Avicel 102	20.3	47.2	53.65	42.45	42.275
Weight per tablet	200.0 mg	300 mg	350 mg	350 mg	350 mg

Evaluation of domperidone ODT. Samples from the prepared tablets were evaluated for their physical, organoleptic and functional properties and for the drug content following standard official and nonofficial procedures.[6]

Weight variation. Twenty tablets were selected at a random basis from each batch and average weight was calculated. Then individual tablets were weighed and the individual weight was compared with the average weight to assess the weight variation of the tablets.

Friability. Tablet friability was measured using Erweka Friability Tester at 25 rpm for 4 minutes. The weight of twenty tablets before and after completion of the test was recorded and friability was calculated by the following formula: % friability = [(initial weight – final weight) ÷ initial weight] x 100.

Hardness. The crushing strength of the tablets was measured by Dr. Schleuniger Pharmatron Tablet Tester. Ten tablets from each batch were tested randomly and the average value was calculated.

***In vitro* and *in vivo* disintegration time.** The disintegration time was determined both in the mouth and by using the disintegration test apparatus BP 2007. For *in vivo* test, a panel of five persons was employed for each batch and the average disintegration time was reported. For *in vitro* test, six tablets were taken per batch and the average disintegration time was determined in water medium following BP 2007 procedure.

Drug content. Twenty tablets were weighed and powdered. An amount of the powder equivalent to 10 mg of domperidone was dissolved in 100 ml of 0.1M HCl, filtered, diluted suitably with the same medium and the absorbance was measured at its λ_{max} of 265 nm. The average amount of drug per tablet present in each batch was calculated with the help of appropriate calibration curve constructed from the absorbance values of standard solutions of domperidone reference standard.

Color, taste and mouth feel. A panel of three persons were employed to assess the color, taste and

mouth feeling of the prepared domperidone orodispersible tablets. The human test was performed according to the guidelines of WMA Helsinki declaration[7]. The comments of the panel members were recorded.

RESULTS AND DISCUSSION

Direct compression method is the easiest way to manufacture tablets. In recent times, this technique has been applied to produce fast dissolving tablets because of the availability of improved tablet excipients, especially tablet disintegrants and sugar-based excipients.[4]

Disintegration consideration: Proper use of disintegrants plays a vital role in the successful development of orodispersible tablet formulations. In this study, the super disintegrants sodium starch glycolate (SSG) along with Kollidone CLSF (crossed-linked povidone) were used to achieve fast disintegration property. These excipients have been employed separately by various workers in ODT formulations although combinations have not been utilized extensively.[1-3,8-10] Sodium bicarbonate was also used as a disintegrating aid which helps to rupture the tablet quickly by the generation of carbon dioxide bubbles. The gas is formed when this ingredient reacts with citric acid in presence of salivary water. The disintegrants principally affect the rate of disintegration and hence the dissolution. The optimization of disintegrant concentration is crucial since it has been observed that, below the optimum level, tablet disintegration time is inversely proportional to disintegrant concentration. Above the critical concentration level, disintegration time remains approximately constant or even increases.[4,9] This trend was also observed in the present study as depicted from Figure 2, where total concentration of the disintegrants (SCG and Kollidone CLSF was plotted against corresponding DT of the tablets. Except for F2, DT of all other formulations remained below the recommended limit of not more than 1 mnuite.[10,11] The BP 2007 has not given any limit of DT for ODTs but specifies less than 3 minutes for all types of dispersible tablets.[6] The time required for *in vivo* breakup of tablets within the mouth of volunteers coincided well with the *in vitro* disintegration results as shown in Figure 3. The method of assessing oral disintegration time has also been reported by other workers.[12]

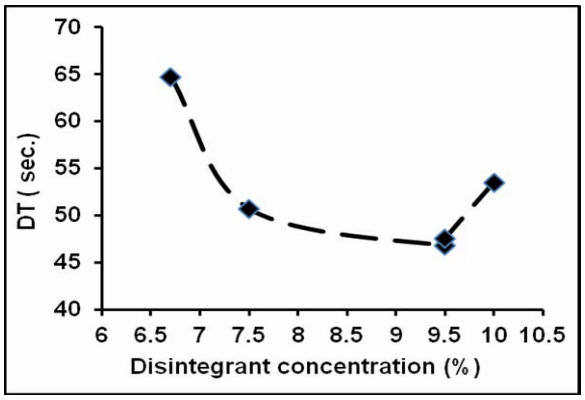


Figure 2. Relationship between disintegrant concentration and disintegration time for the domperidone ODTs

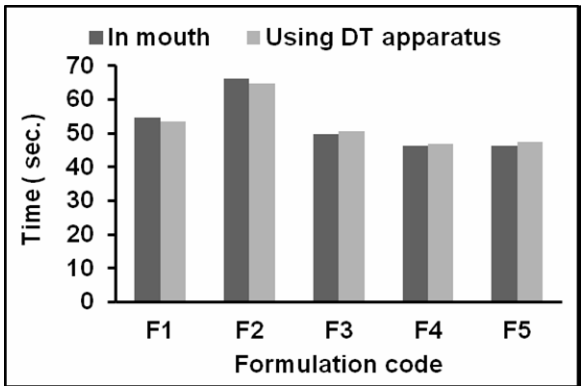


Figure 3. *In vitro* and *in vivo* disintegration time of domperidone ODTs

Hardness and friability considerations: As observed from Table 2**,** hardness value of tablets of F1 was found lower and friability was higher than required. In order to optimize hardness and friability, the amounts of ingredients were successively increased in the subsequent formulations. Although there is no official specification of tablet hardness, a range of 4 to 6 kg / cm^2 may be considered as satisfactory for orodispersible tablets. The friability should also remain below 1.0% for better physical stability. Tablets of formulations F2, F3, F4 and F5 gave satisfactory results in terms of hardness and

friability, and are indicative of sufficient mechanical strength which can withstand stresses of packaging, transportation and handling without adversely affecting the disintegration property.[1-3,6,9]

Organoleptic consideration: The most critical step of ODT formulations in terms of achieving patient compliance and satisfaction is the optimization of taste and mouth-feel. This becomes more important when dealing with bitter drugs like domperidone. Saccharin sodium and aspartame along with citric acid were used to provide sweetness and good mouth-feel as well as to mask the bitter taste of the drug. Sugar based diluents, namely lactose and mannitol, were used to further improve the taste. These sugar based diluents also provide the necessary bulk volume and physical properties of the tablet apart from imparting better mouth feeling to the patient. Particularly, mannitol imparts multi-dimensional benefits as it has good aqueous solubility and good wetting properties facilitating tablet breakdown as well as negative heats of solution giving cooling effect in the mouth.[2] The amounts of these ingredients were increased gradually until the testing panel gave satisfactory comments about their perception of taste and mouth feeling. Although the taste of F4 was acceptable, a remarkable improvement was observed regarding mouth-feel when 0.05% of menthol was added in formulation F5. Tablets of formulation F1 showed mottled appearance which again put forward the need of careful addition of colors in ODTs. The problem of mottling, observed in F1, was solved by changing the order of mixing as mentioned in the preparation of tablets.

Table 2. Various properties of domperidone orodispersible tablets

Formulation code	Weight (mg)			Hardness (kg / cm^2)	Friability (%)	Drug content (mg / tablet)
	L	A	H			
F1	198.0	204.0	209.0	2.25	3.22	9.92
F2	294.0	300.0	305.0	4.29	0.92	10.12
F3	347.0	350.8	354.0	5.38	0.34	9.97
F4	347.0	351.0	354.0	5.31	0.31	10.11
F5	355.0	350.7	347.0	5.23	0.26	10.00

L = lowest weight, A = Average weight, H = Highest weight

Table 3. Color, taste and mouth-feel of domperidone orodispersible tablets

Formulation code	Color	Taste and mouth feel		
		Person 1	Person 2	Person 3
F1	Mottling observed	Bitter from beginning to end	Bitter	Very bitter
F2	No mottling	Bitter	Very bitter	Very bitter
F3	No mottling	Good	Bitterness exists but tolerable	Should be improved
F4	No mottling	Good	Should be improved	Bitterness almost masked. Taste must be improved.
F5	No mottling	Good	Very good	Good

Other tests: As observed from Table 2, tablets of all the five batches complied with the BP 2007 weight variation test since weights of all the tablets were within ±5% of the their respective batch average weights. Assay results were also well satisfactory in terms of BP 2007 requirements as content of active ingredient was within 95-105% in all the cases.[6]

CONCLUSION

Orodispersible tablets of domperidone were successfully prepared by direct compression which is the simplest and cost effective method of tablet manufacturing. The use of combination excipients can be utilized effectively for optimizing the desirable features of ODTs, namely disintegration, hardness, friability, taste masking and mouth feel.

Additional advantage of using excipient combination is that the concentration of individual excipient used in the formulation can be lowered with subsequent decrease in their undesirable effects. Saccharin sodium, for example, can be blended with aspartame to eliminate its bitter aftertaste experienced after taking high concentration of this sweetener. Multifunctional excipients like mannitol will also help in the development of ODT formulations. The results of this preliminary study indicate that satisfactory orodispersible tablets of domperidone can be effectively produced by simple formulation and manufacturing approaches. The results can also be extrapolated to other intensely bitter drug by suitable optimization of the suggested formulation which, in turn, will play important role in popularizing and obtaining benefits from orodispersible dosage forms.

ACKNOWLEDGEMENT

The authors are thankful to ACI Pharmaceuticals Limited, Bangladesh for providing necessary facilities to carry out the research work.

REFERENCES

1. Furtado, S., Deveswaran, R., Bharath, S., Basavaraj, B.V., Abraham, S. and Madhavan, V. 2008. Development and characterization of orodispersible tablets of famotidine containing a subliming agent. *Trop. J. Pharm. Res*. **7**, 1184-1189.
2. Singh, J. and Singh, R. 2009. Optimization and formulation of orodispersible tablets of meloxicam. *Trop. J. Pharm. Res*. **8**, 153-159.
3. Khalid, K.A., Ahmed, A.H., Mowafaq, M.G. and Alaa, A.A. 2010. Formulation and optimization of orodispersible tablets of diazepam. *AAPS PharmSciTech*. **2**, 356-361.
4. Ghosh, T., Ghosh, A. and Prasad, D. 2011. A review on new generation orodispersible tablets and its future prospective. *Int. J. Pharm. Pharm. Sci*. **3**, 1-7.
5. U.S. National Library of Medicine: Drug Information Portal - Domperidone(http://druginfo.nlm.nih.gov/drugportal/dpdirect.jsp?name=Domperidone).
6. British Pharmacopoeia 2007. The Stationery Office on behalf of the Medicines and Healthcare products Regulatory Agency (MHRA). Volume 1, Monographs - Medicinal and Pharmaceutical Substances: Domperidone and Volume 1V, Appendices.
7. World Medical Association Declaration of Helsinki. 1964. Ethical principles for medical research involving human subjects. Adopted in the 18th WMA General Assembly and subsequent amendments.
8. Kulkarni, M.S., Zeeshan, A., Bhise, K.S. and Somwanshi, S.V. 2010. Formulation and evaluation of orodispersible tablet of ornidazole. *Int. J. Pharm. Stud. Res*. **1**, 39-47.
9. Sreenivas, S.A. 2005. Orodispersible tablets: New-fangled drug delivery system - A Review. *Indian J. Pharm. Educ. Res*. **39**, 177-181.
10. Radke, R.S., Jadhav, J.K. and Chajeed, M.R. 2009. Formulation and evaluation of orodispersible tablets of baclofen. *Int. J. Chem. Tech. Res*. **1**, 517-521.
11. Bandari, S., Mittapalli, R.K., Gannu, R. and Rao, Y.M. 2008. Orodispersible tablets: An overview. *Asian J. Pharm*. **2**, 2-11.
12. Ibrahim, H.K. and El-Setouhy, D.A. 2010. Valsartan orodispersible tablets: Formulation, *in vitro*/*in vivo* characterization. *AAPS PharmSciTech*. **11**, 189-196.