Formulation Development and Polymer Optimization for Once-Daily Sustained Release Matrix Tablets of Domperidone

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Abstract

Domperidone is a dopamine receptor blocking agent, which acts on the dopamine receptors in the chemo-emetic trigger zone produces an anti-emetic effect. The purpose of this study was to develop and optimize the polymer for once-daily sustained release matrix tablets of domperidone. The tablets were prepared by the wet granulation method. Aqueous solution of polyvinyl pyrrolidone was used as granulating agent along with hydrophilic matrix material like HPMC, IM-OR-023 and acrylic polymer e.g. Eudragit RS PM. The granules were evaluated for angle of repose, bulk density, compressibility index and drug content. The tablets were subjected to thickness, hardness, friability,, weight variation test, drug content and in vitro release studies. The granules showed satisfactory flow properties, compressibility, and drug content. All the tablet formulations showed acceptable pharmacotechnical properties and drug release profile. The results of dissolution studies indicated that formulations having different weight ratios of IM-OR-023; and in combination of HPMC with Eudragit could extend the drug release up to 24h. Formulation with drug: IM-OR-023 (1:0.48) was the best formulation of the study, exhibited satisfactory drug release in the initial hour and the total release pattern was very close to the theoretical release profile.

Keywords : Sustained release tablet, Domperidone SR tablet, HPMC, Eudragit, anti-emetic tablet

Introduction

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to promptly achieve and then maintain the desired drug concentration. This idealized objective points to the two aspects most important to drug delivery, namely spatial placement and temporal delivery of a drug. Spatial placement relates to targeting of a drug to specific organ or tissue, while temporal delivery refers to controlling the rate of the drug delivery to the target tissue. An appropriately designed sustained release drug delivery system can be a major advance toward solving these two problems. It is for this reason that the science and technology responsible for development of sustained release pharmaceuticals have been and continue to be the focus of a great deal of attention in both industrial and academic laboratories. There currently exist numerous products on the market formulated for both oral and parenteral routes of administration that claimed sustained or controlled drug delivery.[1] Over the past 30 years, as the expense and complications in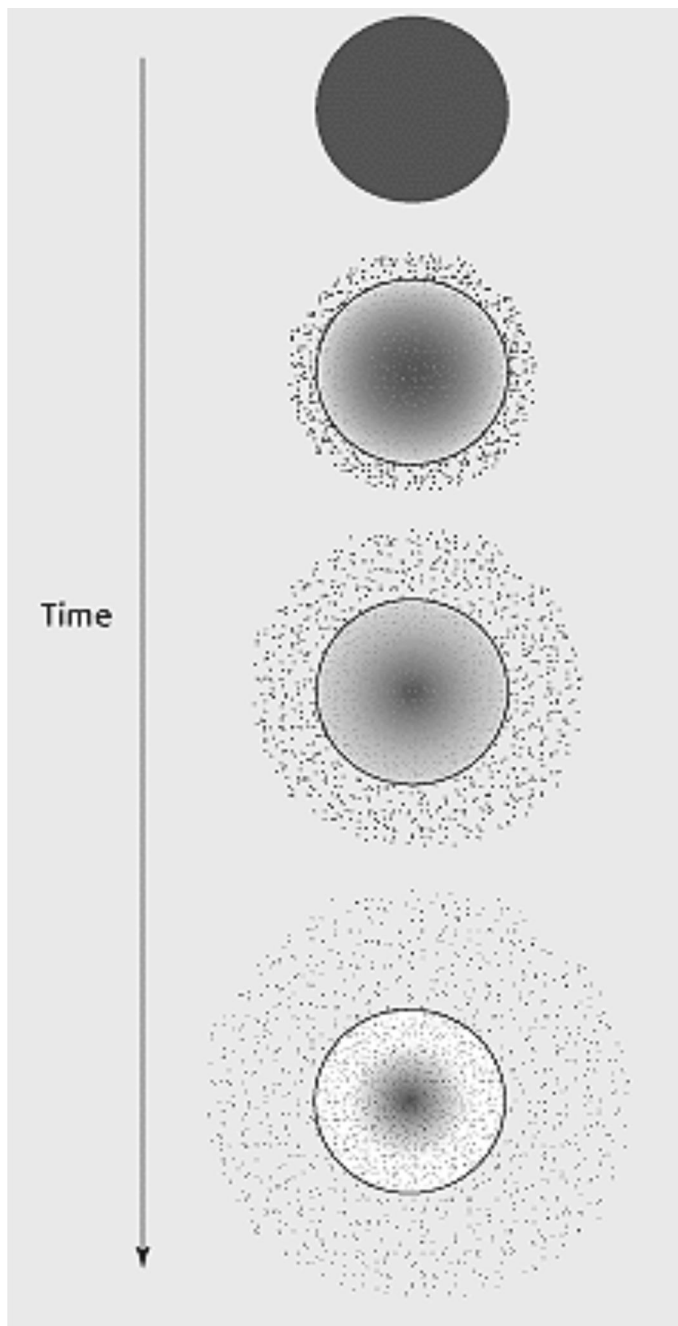volved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled-drug delivery, greater attention have been focused on development of sustained or controlled-release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist. If one was to imagine the ideal drug delivery systems, two prerequisites would be required. First it would be a single dose for the duration of treatment, whether it is for days or weeks, as with infection, or for the lifetime of the patient, as in hypertension or diabetes. Second it should deliver the active entity directly to the site of action, thereby minimizing or eliminating side effects. This may be necessitating delivery to specific receptors or to localization to cells or to specific areas of the body. Sustained release constitutes any dosage form that provides medication over an extended time. Controlled release however, denotes that the system is able to provide some actual therapeutic control, whether this is of a temporal nature, spatial nature, or both. In other words the system attempts to control drug concentrations in the target tissue. This maintenance of drug levels in tissues of the body. Simple definition of sustained release drug systems as any drug or

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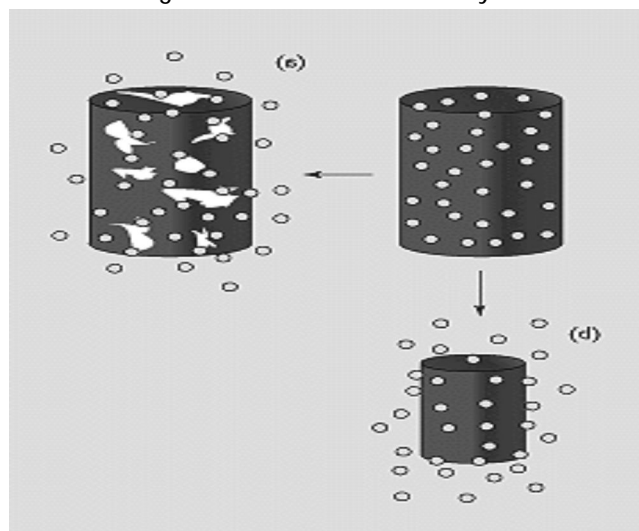**Fig. 1:** Drug delivery from a typical matrix drug delivery system

shown in Fig.1.

It is also possible for a drug delivery system to be designed so that it is incapable of releasing its agent or agents until it is placed in an appropriate biological environment. Swelling-controlled release systems are initially dry, and when placed in the body will absorb water or other body fluids and swell. The swelling increases the aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into the external environment. Example of this type of device is shown in Fig. 2.
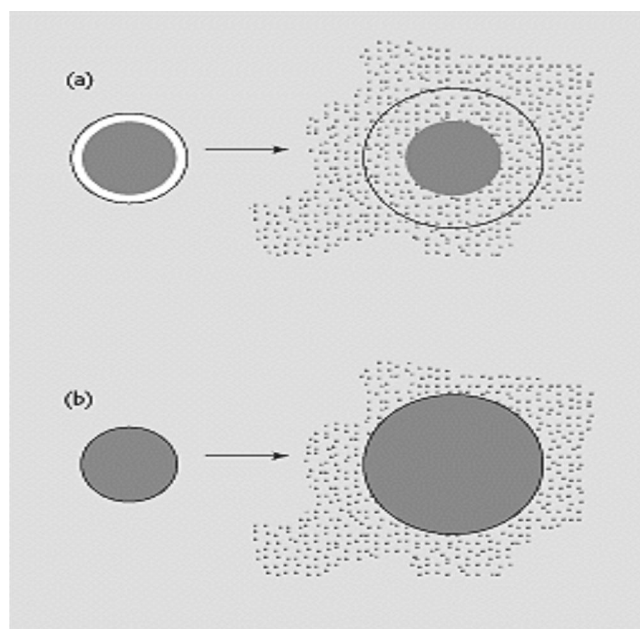
Fig. 2: Drug delivery from (a) reservoir and (b) matrix swelling-controlled release systems.

All of the previously described systems are based on polymers that do not change their chemical structure beyond

dosage form modification that prolongs the therapeutic activity of the drug. Further in the absence of suitable clinical evidence of this sustaining effect we shall accept prolongation of drug levels in the blood.[3]There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, degradation, and swelling followed by diffusion. Any or all of these mechanisms may occur in a given release system. Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. The diffusion can occur on a macroscopic scale-as through pores in the polymer matrix-or on a molecular level, by passing between polymer chains. Example of diffusion-release system is

Fig. 3: Drug delivery from (a) bulk-eroding and (b) surfface -eroding biodegradable systems

what occurs during swelling. However, a great deal of attention and research effort is being concentrated on biodegradable polymers. These materials degrade within the body as a result of natural biological processes, eliminating the need to remove a drug delivery system after release of the active agent has been completed. Example of this type of device is shown in Fig.3.

Domperidone is dopamine–receptor blocking agent in the chemo-emetic trigger zone presently considered the effective drug for the treatment of nausea and vomiting in patients receiving cytostatic and radiation therapy. The biological half-life of domperidone is 7 h and dosage 10 mg 3-4 times per day.

Nausea and vomiting occurs in approximately one third to two third of patients taking opioids. Prevention and control of nausea and vomiting are paramount in the treatment of cancer patients. Nausea and vomiting can result in degeneration of self-care and functional ability, deterioration of patient's mental and physical status. Despite advances in pharmacologic and non-pharmacologic management, nausea and vomiting remain two of the more distressing and feared side effects to cancer patients and their families and incidence may be underestimated by physicians and nurses. Patients receiving radiation to the GIT or brain have the greatest potential for nausea/vomiting as a side effect. Because cells of GIT are dividing quickly and they are quite sensitive to radiation therapy. So, multiple dose administration at intervals of 7h is difficult for a vomiting patient which can lead to patient noncompliance. So, reduction in doses frequency is desirable for patient compliance. Also domperidone is not available for parenteral formulations.12-16 So, with all evident advantages domperidone proved to be a suitable candidate for development of a sustained-release dosage forms. In this study, sustained-release matrix tablets of domperidone were prepared. Mainly three polymers were used to formulate matrix tablets i.e. HPMC, IM-OR-023 and acrylic polymer Eudragit RS PM. IM-OR-023 is a polymer blend of HPMC.

Materials and Methods

Materials

Domperidone BP was purchased from Ranit Pharma Ltd., HPMC 15 cps from Bharat Chemicals Company, IM-OR-023 from Ideal Cures Ltd. and Eudragit RSPM from Rohm Pharma GmbH. Lactose was purchased from Neelraj Agencies, PVP K-30 from Prime Pharmachem, Magnesium stearate from Quality chemicals industries and talc from Mukesh Chemicals. All other reagents were of analytical grade.

Formulation methods

Various formulation variables were taken into account for the polymer optimization for Domperidone sustained release tablets.

By using three formulation variables such as % of HPMC 15cps, % of Eudragit RS PM and % of IM-OR-023 as the factors of the design we got a number of formulations that are mentioned in the following Table 1.

Preparation of the sustained release matrix tablets

The weighed quantity of drug, polymer and lactose were passed through sieve 40 and then 60 and mixed in geometric proportion using a mortar and pestle. PVP was used as binding agent with water. The granules obtained were dried at 50^0C for 30 min. The dried granules were passed through sieve 22–25. Magnesium stearate and talc were passed through sieve 60 and added to the granules. The lubricated granules were mixed thoroughly and subjected to compression using 13 station tablet punching machine and 7 mm FFBE punches.

Evaluation of the granules[24]

Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation: $\tan \emptyset = h/r$, where, h and r are the height and radius of the powder cone.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in the volume was noted. LBD and TBD were calculated using the following formulas:

LBD = weight of the powder / volume of the packing TBD = weight of the powder /tapped volume of the packing

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index:

Carr's index (%) = [(TBD – LBD) * 100] / TBD

Evaluation of tablets[24]

Table 1: Formulation of SR tablets

Formulation No.	Drug: HPMC	Drug: IM -OR- 023	Drug: Eudragit RS PM	Lubricant (mg)
F-1	1:0.75	-	-	1.17
F-2	1:0.86	-	-	1.17
F-3	1:0.95	-	-	1.17
F-4	1:1.05	-	-	1.17
F-5	1:1.19	-	-	1.17
F-6	1:1.05	-	1:0.33	1.17
F-7	1:1.05	-	1:0.29	1.17
F-8	1:1.05	-	1:0.23	1.17
F-9	-	1:0.71	-	1.17
F-10	-	1:0.57	-	1.17
F-11	-	1:0.52	-	1.17
F-12	-	1:0.48	-	1.17
F-13	-	1:0.38	-	1.17
F-14	-	1:0.24	-	1.17
F-15	-	1:0.50	-	1.17

Thickness

The thickness of the tablet was determined using a thickness gauge (Mitutoyo). Six tablets from each batch were used and average values were calculated.

Weight variation test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method. The USP limit for weight ariation in case of tablet weight between 130 to 324 mg is ±7.5%.

Hardness and friability

For each formulation the hardness of 6 tablets was determined using tablet hardness tester. The friability of 20 tablets was determined using Roche friabilator. The limit for friability is NMT 1%.

Drug content

Carry out the method for liquid chromatography. Solution 1: Prepare a solution containing 0.02% w/v of domperidone in methanol, mix with the aid of ultrasound for 20 min and filter through a glass microfibre filter (Whatman GF/C is suitable). To 50 ml of the filtrate, 1 ml of 0.1 (M) HCl acid was added and sufficient water to produce 100 ml. Solution 2: Contains 0.0127% w/v of domperidone BPCRS in a mixture of equal volume of 0.002 (M) HCl acid and methanol. The absorbance was measured at 280 nm.

Table 2: Theoretical drug release profile

Time (h)	% Drug Release
1	15-40
4	30-60
8	55-85
20	NLT 80

Table 3: In vitro drug release profile of Domperidone SR tablets of formulations (F1-F3)

Time (h) %	% Drug Release (F-1)	% Drug Release (F-2)	% Drug Release (F-3)
0.25	92.10	87.13	20.31
0.5	91.60	88.79	23.33
1	93.56	89.42	27.99
4	94.24	90.56	91.86

Table 4: In vitro drug release profile of Domperidone SR tablets of formulations (F4 -F5)

Time (h) %	% Drug Release (F-4)	% Drug Release (F-5)
0.25	13.96	14.22
0.5	18.15	16.10
1	20.63	19.47
4	84.89	84.66
6	91.48	94.88

Table 5: In vitro drug release profile of Domperidone SR tablets of formulations (F6-F15)

Time	% Drug Release									
(h)	F-6	F-7	F-8	F-9	F-10	F-11	F-12	F-13	F-14	F-15
1	18.00	19.15	18.36	14.01	12.03	15.84	20.34	18.23	18.30	17.74
4	26.82	31.21	31.86	24.08	31.06	31.01	35.85	40.92	56.15	31.89
8	40.95	49.02	54.80	45.24	55.01	55.17	60.92	95.94	92.74	56.01
24	80.76	85.55	92.18	78.16	97.86	98.33	96.82	-	-	97.57

Table 6: In vitro drug release profile of the optimized formulation (F-12)

Time	% Drug Release Trial I	% Drug Release Trial II	% Drug Release Trial III	% Drug Release Mean	SEM	SD
1	19.37	20.75	20.90	20.34	0.48	0.84
4	35.74	36.21	35.60	35.85	0.17	0.31
8	61.53	60.31	60.92	60.92	0.35	0.61
24	97.20	96.25	97.01	96.82	0.28	0.49

In vitro release studies[38]

In vitro dissolution studies for all the formulations were carried out using USP apparatus type II at 100 rpm. The dissolution medium consisted of hydrochloric acid buffer solution pH1.2 (900ml), maintained at 37 ± 0.5^{0}C. The drug release at different time intervals was measured by UV-1700 UV-visible spectrophotometer at 284 nm. It was made clear that none of the ingredients used in the matrix formulations interfered with the assay.
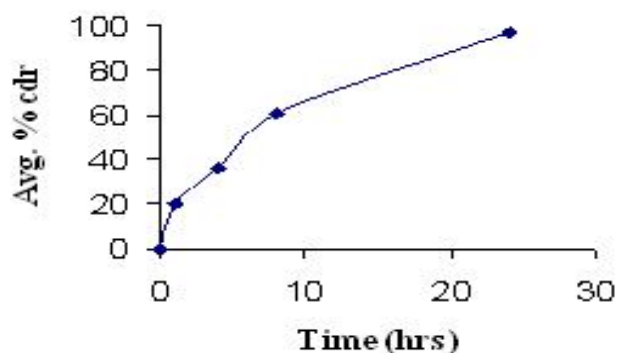
Results

All formulations were tested for in-vitro drug release and the results are represented in the following tables as a function of time (h).

Discussion

The granules for tablet preparation were prepared by wet granulation technique. Physical properties of granules such as specific surface area, shape, hardness, surface characteristic and size can significantly affect the rate of dissolution of drugs contained in a heterogeneous formulation. The granules of optimized formulation were evaluated for angle of repose, compressibility index and drug content. The result of angle of repose between 25 and 30º indicates good flow properties of the granules. This was further supported by lower compressibility index values. Generally compressibility index values up to 15% result in good to excellent flow properties. Granules density, porosity and hardness are often interrelated properties. In addition granule density may influence compressibility, tablet porosity, dissolution and other properties. The drug content in the weighed amount of granules of all batches of optimized formulation was found to be uniform. All these results indicate that the granules possessed

satisfactory flow properties, compressibility and drug content. The tablets of different batches of optimized formulation were subjected to variousevaluation tests such as thickness, hardness, friability, uniformity of weight, drug content in vitro dissolution. All batches showed uniform thickness. In a weight variation test the pharmacopoeial limit for the percentage deviation for tablets weighing between 130-324 mg is $\pm 7.5\%$. The average % deviation of all tablets batches was found to be within the above limit and uniformity of drug content was found among different batches of the tablets and the % of drug content was more than 95%. The hardness of all the tablets batches was found to be uniform. Another measure of tablet strength is friability. Conventional   compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the % friability of all the batches was below 1%, indicating that the friability is within the prescribed limit. All the batches showed acceptable pharmaco- technical properties. In vitro drug release characteristics were studied in pH1.2 hydrochloric acid buffer for 24h using USP dissolution test apparatus type-II. The results of dissolution studies indicated that formulation F-1, F-2 and F-3 released 93.56%, 89.42% and 27.99% at the end of 1 h; and 94.24%, 90.56% % 91.86% at the end of 4 hrs. In an attempt to prolong the release of drug, the concentration of polymer (HPMC) was increased. But the formulation F-4 and F-5 also released 95% of the drug within 6h. HPMC alone could not retard the drug release, so a combination polymer of HPMC and E-RS PM was used. For F-6 and F-7 release was less than the prescribed limit but the release was retarded up to 24 h and hence to get better drug release E-RS PM concentration was increased. Drug release of F-8 was near about close to the theoretical release. But as the polymer E-RS PM is very expensive, this was not economical. So polymer switch over was done from E-RS PM to IM-OR-023. IM-OR-023 I is a mixture of various grades of HPMC. Formulation F-9 and F-10 retarded the drug release up to 24 h but high deviation in the drug release profile from theoretical release pattern which demonstrated the need for further development to find a suitable formulation to mimic the theoretical release pattern. Polymer concentration was reduced in the further formulation. Formulation F-12 showed the satisfactory drug release. To optimize the polymer concentration again three trials were taken. Formulation F-13 and F-14 could not retard the drug release up to 24h due to lower polymer concentration. Formulation F-15 retarded the drug release up to 24h. But F-12 was very close to theoretical drug release. So, the in-vitro drug release pattern showed that the formulation F-12 was the optimized formulation among the matrix tablets developed in the present study.

Fig. 4: In vitro drug release profile of Domperidone SR tablets of the optimized formulation (F-12)

Conclusion

The hydrophilic matrix of HPMC alone could not control the domperidone release effectively for 24 hrs. It is evident from the results the that matrix tablets prepared from HPMC along with acrylic polymer Eudragit RS PM is a better system for once-daily sustained-release matrix tablet of domperidone. But, Eudragit is very expensive material and it is not cost-effective from commercial point of view. The formulation with IM-OR-023 showed effective drug release and this was commercially cost effective. Formulation F-12 exhibited satisfactory drug release in the initial hours and the total release pattern was very close to the theoretical release profile. So, F-12 was the most successful, cost-effective and optimized formulation.

Acknowledgements

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