Formulation and Development of Orodispersible Sustained Release Tablet of Domperidone

Authors

Hemlata G. Patil[1], Roshan Tiwari[2], Michael A Repka[2] and Kamalinder K. Singh[1,3]*

Address

[1] C.U.Shah College of Pharmacy, SNDT Women's University, Mumbai 400049, India.

[2] Department of Pharmaceutics & Drug Delivery, University of Mississippi, Mississippi 38677, USA

[3] School of Pharmacy and Biomedical Sciences, University of Central Lancashire, Preston, PR1 2HE, UK

*Corresponding author; Tel. No.: +441772895843

e-mail: ksingh1@uclan.ac.uk

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Abstract: Commercially available domperidone orodispersible tablets (ODT) are intended for immediate release of the drug but none of them have been formulated for sustained action**.** The aim of the present research work was to develop and evaluate orodispersible sustained release tablet (ODT-SR) of domperidone, which has the convenience of ODT and benefits of controlled release product combined in one. The technology comprised of developing sustained release microspheres (MS) of domperidone, followed by direct compression of MS along with suitable excipients to yield ODT-SR which rapidly disperses within 30 seconds and yet the dispersed MS maintain their integrity to have a sustained drug release. The particle size of the MS was optimized to be less than 200 μm to avoid the grittiness in the mouth. The DSC thermograms of MS showed the absence of drug-polymer interaction within the microparticles, while SEM confirmed their spherical shape and porous nature. Angle of repose, compressibility and Hausner's ratio of the blend for compression showed good flowability and high percent compressibility. The optimised ODT-SR showed disintegration time of 21 seconds and matrix controlled drug release for 9 h. *In-vivo* pharmacokinetic studies in Wistar rats showed that the ODT-SR had a prolonged MRT of 11.16 h as compared 3.86 h of conventional tablet. The developed technology is easily scalable and holds potential for commercial exploitation.

Keywords: Antiemetic, orodispersible tablet, microspheres, sustained release.

Introduction

Oral tablets have been the most popular and successfully used dosage form for delivery of drugs because of the convenience for use, ease of administration, simplicity in production and low cost of such systems. However, problems may arise in the administration of tablets to patients who have difficulty in swallowing, for example children, elderly people or more seriously ill patients. Orodispersible tablet (ODT) is good for such subpopulations, in general for paediatric and geriatric patients[1] or patients with swallowing dysfunction or dysphagia[2]. ODTs disintegrate in the oral cavity within seconds and are washed out with saliva without the need of liquid[3]. These tablets are also suitable for those who are travelling and do not have easy access to water, mentally ill, bedridden and patients with persistent nausea[4-6]. It is also useful for the patients, where the underlying disease disrupts swallowing ability (e.g. migraine, Parkinson's disease)[7-9]. Studies have shown distinct patient preference for ODTs over regular tablets in certain disease conditions[10-12].

ODTs by virtue of their fast disintegration are meant for immediate release of drug. Though these tablets cater to patients with swallowing difficulties and other patient needs as outlined above however, they are required to be administered frequently, depending upon the biological half-life of the drug and may lead to poor patient compliance. This limitation can be overcome by designing sustained release (SR) or controlled release drug delivery system[13-15]. The current sustained release technologies can be exploited and incorporated into an ODT to improve their functionality reducing need of multiple dosing regimens, improving patient adhereance, provide predictable and reproducible drug release, maintain steady drug plasma levels and reduce dose-dependent side effects associated with the repeated administration[16].

Domperidone (5-chloro-1-[1-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)propyl]piperidine-4-yl]-1,3-dihydro-2H-benzimidazol-2-one; (Figure 1), is a weak base (pKa=7.89), practically insoluble in water and with a lipid to water ratio (log P) of 3.90[17]. It is a potent drug exerting its gastrokinetic action by acting on the peripheral dopamine.sub.2 receptors in the GIT and is a unique compound with both gastrokinetic and antiemetic activity[18,19]. Unlike metoclopramide, another dopamine-receptor antagonist, domperidone does not readily cross the blood-brain barrier; therefore it has rather minimal extrapyramidal side effects. Clinically, domperidone has been shown to be useful in the treatment of various gastric motility disorders, namely chronic and subacute gastritis, to prevent GI symptoms associated with the use of dopamine agonists in Parkinson's disease, in diabetic gastroparesis, in anorexia nervosa and in patients with postvagotomy gastroparesis[20]. Commercially available orodispersible domperidone tablets are meant for immediate release of the drug and are given 3-4 times a day due to the short half-life (~7 h).

One of the approaches to prepare controlled release formulations is the use of microsphere (MS) or microparticles of drug-polymer composites, where the active ingredient is distributed in the polymer matrix[21,22]. The polymeric matrix allows for slow, controlled and predictable drug release over a period of time and hence reduces the overall amount of drug needed to be incorporated[23,24]. The present work reports development of orodispersible sustained release tablets (ODT-SR) of domperidone which includes, first the preparation of sustained release MS of domperidone which were then compressed along with suitable excipients to give orodispersible sustained release tablet with the desired characteristics. This tablet is intended to disintegrate rapidly within the mouth into microspheres which will deliver the drug in a sustained manner after swallowing. For better

patient-compliance, after disintegration of the tablet in the mouth, the disintegrated material should be small in particle size, so that patients do not feel the unpleasant grittiness of bigger particles. The maximum particle size with which patients do not feel the sandy feeling or rough sensation on the tongue is around 200 µm, so the particle size of MS was envisaged to be less than 200 µm to avoid any rough mouth feel[25]. Such a formulation would have all the advantages and convenience of ODT dosage form and would simultaneously provide sustained release of the drug. Furthermore, although orodispersible tablet with sustained release properties is reported[26-29] incorporating MS prepared by emulsion solvent evaporation technique into ODT has not been investigated. MS of domperidone are very easy to prepare by this emulsion solvent evaporation technique and can be beneficial commercially.

Materials and Methods

Materials

Domperidone was obtained as a gift sample from Ipca laboratories Ltd, Mumbai. Avicel (FMC Biopolymer), Pearlitol 200 SD (Roquette), lactose, Polyplasdone XL-10, sodium saccharine, magnesium stearate (Ferro), Aerosil 200 were received as gift samples from Signet Chemicals, Mumbai. Ethocel Std. 10 was a gift sample from Dow, India. Directly compressible microcrystalline cellulose (Avicel PH- 102, particle size ~100 µm) was gift from FMC Biopolymers, India. Ethanol, Span 80, liquid paraffin and n-hexane were purchased from S.D. Fine chemicals, Mumbai. Domilon-MD® (Senate Labs) and Domperi- 10® (Saorite Phamracetuicals) were purchased from a local pharmacy in Mumbai.

Methods

Formulation of ODT-SR

Formulation of ODT-SR involved two steps:

a) Preparation and characterization of sustained release MS of domperidone

b) Preparation of ODT-SR incorpoarating domperidone MS

Preparation of Sustained Release microspheres

MS of domperidone were prepared by emulsion solvent evaporation method[30,31]. Formulations were prepared by varying drug: polymer ratios. Drug and polymer were dissolved in ethanol. The above mixture was added dropwise with help of syringe in light liquid paraffin and stirred at 2000 rpm for four hours. The formed MS were vacuum filtered and then freed from liquid paraffin by repeated (2-3 times) washing with n-hexane and further the product was air dried over a period of 12 h to remove completely the traces of n-hexane and sieved through US sieve no. 70. Optimization studies were conducted to investigate the effect of formulation variables on characteristics of domperidone MS. A randomized 3^2 full factorial design was used to optimize the effect of two input variables i.e. polymer concentration (X_1) and drug concentration (X_2) in the MS on three response variables i.e. mean particle size, percent yield and percent drug entrapment (Table 1a).

Characterisation of Domperidone Microspheres

a) Particle Size

Particle size of the MS were characterized using optical microscopy (Olympus microscope, India). Measurement of 200 microspheres was taken and mean particle size and particle size distribution were determined[32].

b) Calibration Curve of the Domperidone

As domperidone is poorly soluble in water, organic solvent is required to solubilize the drug. Therefore, stock solution of domperidone was prepared in methanol and working standards were prepared by suitably diluting with 0.1M HCl and the absorbance were measured using UV-Vis

Spectrophotometer (Jasco, MD, USA) at λmax 287 nm against blank. Calibration curve was plotted between drug concentration (2-20 μg/ml) and absorbance for each of the working standards.

c) Drug Entrapment Efficiency

A weighed quantity of MS were crushed into powder and added to 100 ml of 0.1 M Hydrochloric acid (HCl). The resulting mixture was kept stirring at 1000 rpm for 2 h. Then the solution was filtered through membrane filter of 0.45 μm pore size and 1 ml of this solution was diluted using 0.1 M HCl and analyzed for domperidone content using UV Spectrophotometer at λmax of 287 nm. The drug entrapment efficiency was calculated using the following equation:

$$Drug\ entrapment\ efficiency = \frac{Experimental\ drug\ content}{Theoretical\ drug\ content} \times 100$$

d) Percent Yield

The prepared MS were collected and weighed. The weight obtained was divided by the total amount of all non-volatile components which were used for the preparation of the MS.

$$\%\ Yield = \frac{Actual\ weight\ of\ product}{Total\ weight\ of\ excipients\ and\ drug} \times 100$$

e) Scanning Electron Microscopy (SEM)

The surface characteristics of drug loaded MS were examined by means of a scanning electron microscopy. The MS were coated with gold or palladium under vacuum using a sputter coater and then samples were examined under the scanning electron microscope (Philips XL 30 SEM) setup at 10kv with a till of 45°. Using suitable magnification SEM micrographs of domperidone loaded MS were recorded.

f) Differential Scanning Calorimetry (DSC)

Drug-polymer interactions were studied by DSC (Q 2000 TA Instruments) analysis. The DSC analysis of pure domperidone, ethyl cellulose and domperidone MS was carried out by heating samples in the range of 30 to 340 ^{0}C at a rate of 10 ^{0}C min $^{-1}$ and the thermograms were recorded.

g) *In-vitro* Drug release

100 mg of drug loaded MS were tied in nylon cloth and kept in the basket which was then immersed in the dissolution medium (0.1 M HCl, 900 ml) and stirred at 100 rpm using USP dissolution Apparatus II (Electrolab EDT-08Lx). 5 ml of aliquots of medium were removed after 30 min, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 h respectively, each aliquots being replaced simultaneously by an equal volume of medium to maintain constant volume. The amount of domperidone was determined spectrophotometrically using UV spectrophotometer at λmax 287 nm. The test was carried out in triplicate. The amount of drug released was calculated using standard calibration curve of the drug in 0.1 M HCl. The drug release profiles for various MS formulations were plotted as the percent of domperidone released from the MS vs. time and further studied for the release kinetics.

h) Drug Release Kinetics

 To determine the mechanism of drug release from MS, data were subjected to further analysis. The data were fitted to zero order (equation 1), first order (equation 2) and Higuchi's matrix diffusion controlled (equation 3) kinetics[33,34].

$Q_t = Q_0 - K_0t$ ……………................Equation 1

$\log Q_t = \log Q_0 − K_1t/2.303$ ………...Equation 2

$Q_t = K_Ht^{1/2}$ ....Euation 3

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in the solution, K_0 is the zero order release rate constant, K_1 is the first order release rate constant, K_H is the Higuchi diffusion rate constant, and geometrical characteristics of the tablets.

Formulation and Evaluation of ODT-SR

The formulation of ODT-SRs involved preparation and evaluation of dry blend of MS with suitable excipients for compression followed by direct compression into tablets.

Preparation and Physical Characterization of Blends Ready for Compression

MS were dry blended in a tumbling cylindrical blender with suitable excipients like mannitol (diluent), lactose (diluent), microcrystalline cellulose (diluent) crospovidone, (super disintegrant), magnesium stearate (lubricant), sodium saccharine (sweetner) and Aerosil (glidant) to prepare seven batches (F1-F7) with various compositions (Table 2). The blends ready for compression were evaluated for various physicochemical characteristics such as angle of repose, bulk density, tapped density, percent compressibility and Hausner's ratio.

Preparation and Evaluation of ODT-SR

A single punch tablet compression machine (Cadmach Company, India), equipped with flat faced punches with a die diameter of 8 mm was employed to prepare tablets with an average weight of 200 mg. ODT-SRs were evaluated for the following parameters:

a) Uniformity of Mass for Single-dose Preparations

The individual and average weight of 20 tablets from each batch was determined using an electronic balance and conformity to uniformity of mass test for tablets for each batch was established[35]. The average mass was expressed in mg ± S.D.

b) Thickness of Tablets

Thickness of tablets was assessed using a Vernier caliper (Fisher Scientific, USA).

c) Hardness

The Monsanto hardness tester was used to measure the crushing strength of the tablets. The average hardness (mean of three determinations) was calculated.

d) Drug Content

Domperidone content in the ODT-SR was determined. Briefly, 20 tablets were selected randomly and triturated with the help of morter and pestle. The amount equivalent to weight of one tablet was weighed and domperidone content was determined using UV-Vis Spectrophotometer at λmax 287 nm against blank.

e) Friability

According to European Pharmacopoeia[35], sample of twenty tablets was accurately weighed and placed in the drum of tablet friability tester (Electrolab EF-1W India) revolving at 25 rpm for 4 min. At the end of the 100 rotations, the tablets were removed, dusted and reweighed to determine the loss in the weight of the tablets.. The percentage friability was determined using the following equation:

$$Friability\ (\%) = \frac{Final\ weight - Initial\ weight}{Initial\ weight} \times 100$$

f) Disintegration Time

The mean disintegration time for six ODT-SRs were determined in seconds (±S.D).

g) *In-vitro* Drug Release

In-vitro drug release from ODT-SR was studied using USP type II dissolution test apparatus (Electrolab EDT-08Lx) in 900 ml of 0.1 M HCl maintained at $37 \pm 0.5\ ^0C$ with paddle speed of rotation of 100 rpm. Domperidone content was analyzed at λmax of 287 nm using UV-Vis spectrophotometer.

h) Stability Study

The stability of the developed ODT-SR was conducted for 12 weeks. Optimized formulation (F4) was selected for the stability study. Briefly, samples were stored in the sealed aluminium pouch at 25°C/60% RH and at 40°C/75% RH. Samples were analyzed for appearance, domperidone content and drug release profile during the stability study duration of 12 weeks.

i) *InVivo* Pharmacokinetic Study

Pharmacokinetic study of optimized ODT-SR (F4) was carried out in Wistar rats after oral administration and compared with a conventional marketed domperidone tablet (OC2). The protocol of the study was approved by the Institutional Animal Ethics Committee of C.U.Shah College of Pharmacy, SNDT Women's University, Mumbai.

i) Animal Specification

Wistar rats weighing about 180-220 g were used for the study. Animals were fed with a standard pelletised diet and were given free access to water.

ii) Drug Administration and Collection of Plasma

The ODT-SR of domperidone was administered orally at a single dose of 1.64 mg/ 200 g body weight after dispersing it in normal saline[36]. Necessary corrections were made and the animal dosage was determined from the human dose using the conversion factor[37]. An identical dose was given for the marketed domperidone tablet. The marketed domperidone tablet was grinded and dispersed in 1.5 ml of 0.5% (w/v) carboxymethylcellulose–sodium (CMC–Na) solution and tablet suspension was administered to rat by oral gavage[38]. After administration of the formulations, blood was withdrawn using the sparse withdrawal technique at suitable intervals of 0.5, 1, 2, 4, 6, 8, 10, 14, 15 and 24 h from the retro-orbital plexus of the rat eye. For withdrawal of blood from

retro-orbital plexus, the animals were exposed to chloroform vapors and made unconscious temporarily and the blood was withdrawn using fine capillary and collected in a test tube containing 0.3% sodium citrate solution as an anticoagulant. Blood was centrifuged for 10 minutes at 3000 rpm. The supernatant layer of plasma was separated by micropipette and was stored at -20ºC until further analysis.

iii) Extraction of Drug from Plasma

To 500 µl of plasma, 1.5 ml of acetonitrile was added and vortexed for 3 minutes, followed by centrifugation at 3000 rpm. After centrifugation, supernatant layer of acetonitrile was carefully separated and analyzed using a validated HPLC method.

iv) Chromatographic Conditions

Analysis of domperidone in plasma samples was carried out by reverse phase HPLC (Aigilent Technologies 1200 series). The chromatography was carried out using C-18 column (25cm × 4.5 mm, 0.5 µm) at 287 nm wavelength (λ) with a mobile phase of buffer (pH 7.4):acetonitrile (2:1) at flow rate of 1ml/min. The injection volume was kept constant at 10µl and run time was maintained for 20 minutes.

v) Pharmacokinetic Analysis

Standard methods[39] were used to calculate the pharmacokinetic parameters such as area under the drug-concentration time-curve (AUC), half- life ($t1/2$) and mean residence time (MRT) using non-compartmental analysis. The maximum plasma concentration of drug (Cmax) and time to reach Cmax (Tmax) were directly computed from the plasma concentration vs. time plot.

f) Statistical Analysis

Statistical comparisons of the experimental results were performed by one-way analysis of variance (ANOVA) at an alpha level of 0.05. The difference in results between the 2 groups was compared by Tukey-Kramer multiple comparison test at the significance levels of $P < 0.05$.

Results and Discussion

Domperidone Loaded Microspheres

a) Preparation of Microspheres

Ethyl cellulose was used as the polymer for the preparation of sustained release MS. Ethyl cellulose solution at a level of 0.5% w/v or less was not viscous enough to form and/or sustain the formed micro droplets, which is essential for the formation of MS. On the other hand, the polymer solution was found to be too viscous to pass through syringe when used at 3% w/v concentration level and did not yield droplets of desirable size for preparation of MS, but rather resulted in the formation of large aggregates. Therefore, three polymer concentrations, greater than 0.5% w/v and less than 3% w/v viz. 1.5, 2 and 2.5% w/v were investigated for the optimization of preparation of MS along with the second input variable, drug concentration using 3^2 factorial designs and their effect on the mean particle size, percent yield, and percent drug entrapment was observed.

It was observed that with the increase in polymer concentration from lower level (X_1,-1) to higher level (X_1, +1), at all three drug levels (X_2, -1, 0 and +1) resulted in the increase in the mean particle size of MS from 58 to 196 µm. This increase in particle size may be because of the increase in viscosity of the droplets due to the increased polymer concentration. The increase in viscosity was high enough to result in difficulty in dispersion and subdivision of the droplets. Similar effects have been reported for ethylcellulose MS prepared by water-in-oil-in-oil double emulsion solvent

diffusion technique[40]. Increase in drug concentration from lower level (X_2, -1) to higher level (X_2, +1) also resulted in increase in mean particle size of the MS. Increase in mean particle size with the increase in the drug concentration may also be because of the increase in viscosity of the droplets present in the internal phase caused by the increased drug concentration.

Polymer concentration at medium level (X_1, 0) and domperidone at the highest level (X_2, +1) yielded MS with the highest drug entrapment (74%) as well as highest percent yield (86%). When X_1 was set at the medium level (0) and X_2 was set either at the lower (-1) or at the medium level (0), less than 74% of the drug was found to load in the MS and also resulted in lower percent yield.

The effects of the input variables on the % drug entrapment, particle size and percent yield of domperidone ethylcellulose MS were statistically analysed using analysis of variance, ANOVA. The data obtained was then used to generate predictor equations for domperidone concentration and polymer concentration. The results of ANOVA are given in Table 1a.

Percentage drug entrapment of the MS showed a R^2 value of 0.999, indicating a good fit. Also, percent yield and particle size of the MS showed a R^2 value of 0.9997 and 0.9961 respectively indicating a good fit.

Regression of the data resulted in the equations:

$Y_1 = 48.67 - 23.83X_1 - 5.33X_2 - 13.25X_1X_2 - 28.50X_1^2 + 8.00X_2^2$

$Y_2 = 89 - 2.17X_1 - 21.67X_2 - 56.0X_1X_2 - 64.5X_1^2 + 35X_2^2$

$Y_3 = 60 - 22.5X_1 - 14.5X_2 - 29.5X_1X_2 - 18.00X_1^2 + 13.5X_2^2$

Where dependent variables Y_1 is the drug entrapment, Y_2 is the particle size and Y_3 is the percent yield of the domperidone loaded ethyl cellulose MS. Whereas X_1 and X_2 are the independent

variables corresponding to amount of ethyl cellulose (% w/v) and amount of domperidone (% w/v) in MS respectively.

b) Characterization of MS

i)Appearance and Particle size

The MS were white in color, spherical in shape and free flowing with rigid morphology. The MS were in the size range of 45-189 µm with mean particle size of 151 µm (Figure 2a). The particle size of MS was well within ≤ 200 µm limit and would thus avoid any gritty feeling in the mouth

after disintegration.   It is well known that particle size above 200 µm causes rough mouth feel though threshold particle size within ODT required for feeling roughness has been determined to be >200µm because of the palatability of the exicipients like mannitol used in ODT[25,41].

ii) Calibration Curve of Domperidone

Calibration curve of domperidone was prepared in 0.1 M HCl. Equation for calibration curve obtained was y = 0.0375x - 0.051; and a R^2 value of 0.996 estabilished the linearity in the concentration range of 2-20 µg/ml.

iii) Scanning Electron Microscopy

The SEM studies revealed domperidone loaded MS were spherical in shape. However the surface of MS was rough with a porous texture (Figure 2b). This is in confirmation with earlier reports on MS prepared with ethyl cellulose polymer[42,43].

iv) Differential Scanning Calorimetry (DSC)

The drug could be either dispersed in crystalline or amorphous form or dissolved in the polymeric matrix during the process of micro encapsulation. Any abrupt or drastic change in the thermal

behavior of either the drug or polymer may indicate a possible drug-polymer interaction. DSC of domperidone MS (Figure 3) displayed characteristic, well recognizable endothermic peak of domperidone at the 254^0C, temperature corresponding to the melting point of the pure drug indicating that the drug is compatible with the polymer and no significant transformation of the drug has occurred after processing[44]. There was no change in the melting endotherm of the polymer confirming absence of any drug polymer interaction.

v) *In-Vitro* **Drug Release**

Several techniques have been utilized to improve the dissolution of active pharmaceutical ingredient[45]. It has been reported[44] that the dissolution profile of domperidone pure drug in a acidic medium of pH 1.2 buffer showed drug to dissolve to the extent of 91% in 2 h, however, in an alkaline pH the dissolution of the drug was much slower, with as much as only 16% dissolved in 15 min. in buffer of pH 6.8. As maintenance of sink conditions is an important requirement of dissolution media and drug release from the microspheres is the desirable rate limiting factor, dissolution studies were performed in pH 1.2 buffer[46].

In-vitro release of domperidone from ethyl cellulose MS exhibited initial burst release with 23% of drug being released in 1 h. This is a common observation in the MS formulations due to the presence of drug particles on the surface of the MS. The burst effect seen during the *in-vitro* release from the MS was lower in case of MS prepared from higher concentration of the polymer[47,48,]. After the burst release, all the domperidone MS formulations showed sustained release of the drug up to 9 h. The best fit with the highest correlation coefficient was shown in Higuchi equation followed by first-order and then zero-order equation (Table 1b). High correlation observed in the Higuchi plot rather than first-order and zero-order models indicated matrix controlled drug release

kinetics. Previously reported Zidovudine MS prepared using ethyl cellulose has shown similar release profile[42,43].

Orodispersible Sustained Release Tablet

a) Physical Properties of the Tablet Blend

Table 3 reports the evaluation of physical properties like bulk density, tap density, percent compressibility and Hausner ratio of blends ready for compression for all ODT-SR batches. According to literature[49] powders with a percent compressibility between 5 and 18% are suitable for producing tablets and those with a Hausner ratio below 1.25 have good flowability. ODT-SR blends of all batches demonstrated a percent compressibility between 8.37 and 15.04 and a Hausner ratio below 1.25. Percent compressibility and Hausner ratio of ODT-SR blends suggests good compressibility for all formulations, except F5 and F7. The ODT-SR blend of all the batches also showed good flowability (angle of repose <30°), except batch F1 with an angle of 42.16°. The poor flowability of F1 may be attributed to the presence of only microcrystalline cellulose having filamentous particles as a diluent[50].

b) Evaluation of Orodispersible Sustained Release Tablet

The thickness of all the tablets was found in range of 2.37 to 2.41 mm and was within the prescribed limits (±5%)[51]. All tablets were acceptable in terms of uniformity of mass[35]. Friability of all batches was less than 1% and hardness was found to be within the limits specified (35-40 N) for fast disintegrating tablets (Table 4).

i) Disintegration Time

As ODT-SR was formulated as compressed tablet ODT, crospovidone was used as superdisintegrant to provide quick disintegration of the tablet[52]. The time for disintegration for ODT is usually considered less than a minute[53]. However there is lack of globally harmonized

nomenclature and disintegration criteria for ODTs. For example the European Pharmacopoeia[35] defines orodispersible dosage forms as having disintegration time of less than 3 min but US FDA guidelines for ODTs state that ODTs should have *in-vitro* disintegration time of 30 seconds or less[54,55]. The ODT-SR formulations (FI-F7) disintergrated in less than a minute meeting the requirements of the European Pharmacopoeia, batch F4 with disintegration time of 21 seconds also met the more rigrous guidelines of US FDA (Table 4) and was selected for further studies. Spray-dried mannitol and microcrystalline cellulose in the ratio 1:1 in batch F4 contributed to its fast disintegration. The batch F6 containing a higher amount of spray-dried mannitol showed increased disintegration time. Increase in disintegration time may be due to the increase in the polyol quantity in the tablet formulations. As polyols are readily soluble in water, there exists a competition between spray-dried mannitol and Crospovidone for water penetrating into the tablet, consequently leading to poor swelling of Crospovidone with subsequent delay in disintegration. Disintegration time of tablets of batch F5 containing microcrystalline cellulose and spray-dried lactose in a 1:1 ratio was also slightly higher than F4, probably because of the formation of a sticky layer due to the dissolution of the lactose and subsequent hindrance in the further ingress of water into the tablet in accordance with the study of Khan et al[56].

ii) *In-vitro* Drug Release

When the selected ODT-SR (F4) was placed in *in-vitro* release medium it disintegrated rapidly releasing the intact MS. The drug release from these MS was similar to that obtained prior to compression and confirmed the maintenance of integrity of the MS on compression. As observed in the dissolution profile of MS, there was burst release of 23 % in 1 h, 50 % of the drug released in 2.26 h and 90 % of drug was released in 7.53 h. The drug release typically followed Higuchi square root kinetics with sustained drug release up to 9 h. This is totally in contrast with

conventional orodispersible tablets (OC1) of domperidone which released 100 % of the drug in 10 min and while the conventional domperidone tablets (OC2) released the drug in 2 h (Figure 4).

iii) Stability

Stability studies of ODT-SR (F4) stored in an aluminium package under normal temperature and in a controlled stability chamber at 40 ºC and 75% RH for 12 weeks, showed no significant changes in the domperidone content, drug release profile and color of the tablets. The content of domperidone was stable ranging from 97.66% to 98.78% during 12 weeks after storage at 25ºC and 60% RH , or from 98.24% to 98.88% during the same period after storage at 40ºC and 75% RH. Drug release profile of F4 in terms of $t_{10\%}$, $t_{50\%}$ and $t_{90\%}$ was found in the range of 0.29 h to 0.34 h , 2.24 h to 2.34 h and 7.53 h to 7.65 h respectively, during 12 weeks after storage at 25ºC and 60% RH and 0.34 h to 0.39 h , 2.22h to 2.68 h and 7.65 h to 7.81 h respectively, for 12 weeks after storage at 40ºC and 75% RH.

iv) *In-vivo* Pharmacokinetic Studies of Domperidone

Domperidone after oral administration in Wistar rat was absorbed rapidly from the conventional formulation giving a mean peak plasma concentration of 23.53 µg/ml within 4 h after treatment. Domperidone is known to undergo rapid and complete absorption from gut[57,58]. The drug plasma concentration declined rapidly thereafter with no drug being detected beyond 8 h. Domperidone undergoes rapid first pass metabolism though renal clearance is low[59]. Conventional formulation showed much shorter $t_{1/2}$ as compared to that reported for humans. This is consistent with an earlier study showing $t_{1/2}$ of 1.40 ± 0.02 h for domperidone in rat[60].

The ODT-SR (F4) of domperidone gave a mean peak plasma concentration of 20.4266 µg/ml 10 h post administration (Figure 5). The ODT-SR maintained drug concentration in plasma up to 24 h as compared to the conventional formulation, where the drug levels could no longer be detected

after 8 h. It was also observed that MRT of the domperidone ODT-SR (11.16 h) was 2.9 times higher than that of the conventional marketed formulation (3.86 h) indicating prolonged residence in the body. Thus, significant sustained drug plasma levels were observed with ODT-SR indicating rate controlled release of domperidone from the MS after oral administration. when compared to the marketed formulation (Table 5).

The mean AUC of the ODT-SR was 415.3 µg.h/ml, which was almost 3 times greater than AUC obtained with conventional marketed domperidone tablet indicating higher bioavailability of the ODT-SR. Statistical analysis by ANOVA revealed significant difference between two groups in the values of C_{max}, $T_{max,}$ AUC, and MRT as revealed by the F value at 5 DF and $P < 0.05$.

Conclusion

The present platform technology combines the convenience of fast dissolving orodispersible dosage form and performance of controlled release delivery system. Not only would it address some of the problems encountered in administration of drugs to the pediatric and elderly patient, which constitutes a large proportion of the world's population but also has added therapeutic advantages of less frequent administration, patient compliance, predictable and reproducible drug release, steady drug plasma levels with better treatment efficiency.

The ODT-SR of domperidone disperses readily within 21 sec without exceeding the disintegration time limitation specified in the US FDA guidelines for ODT (< 30 sec) into MS of size range of 45-189 µm, which released the drug in sustained manner over the period of 9 h. The *in-vivo* pharmacokinetic study in Wistar rats revealed that the ODT-SR maintained drug concentration in plasma up to 24 h with three times higher bioavailability. Statistical analysis by ANOVA revealed significant difference between marketed conventional tablet of domperidone and ODT-SR. Thus this product has convenience of orodispersible dosage form and a benefits of sustained release

system combined in one. The developed technology is simple and can be easily scaled up and thus, holds enormous potential for commercial exploitation.

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Declaration of Interest

The authors reprt no declaration of interest.

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TABLE LEGENDS

Table No.	Table Legends
Table Ia	3^2 Factorial design to study effect of polymer and drug concentration in MS
Table Ib	Goodness of fit to mathematical drug release models applied to drug release kinetics of MS
Table II	Compositions of ODT-SR of domperidone
Table III	Physical characterization of blends of ODT-SR ready for compression

Table I (a): 3^2 Factorial design to study effect of polymer and drug concentration in MS

Trial No.	X1	X2	Mean particle Size (μ)	Percent Yield	Percent drug entrapment
1	-1	-1	58	75	57
2	-1	0	65	79	68
3	-1	1	86	64	64
4	0	-1	113	79	67
5	0	0	132+	74	62
6	0	1	151	86	74
7	1	-1	196	83	46
8	1	0	----------	Precipitation	-------
9	1	1	---------	Precipitation	-------

Translation of coded levels in actual values

Coded level	-1	0	1
X1: Ethyl Cellulose (% w/v)	1.5	2	2.5
X2: Domperidone (%)	0.5	1	1.5

Table I (b): Goodness of fit to mathematical drug release models applied to drug release kinetics of MS

Trial No	Zero order plot	First order plot	Higuchi's plot
1	0.9117	0.8994	0.99
2	0.9637	0.8047	0.97
3	0.9567	0.8831	0.97
4	0.9691	0.8566	0.97
5	0.9656	0.9079	0.98
6	0.9671	0.9104	0.97
7	0.9459	0.7746	0.98

Table II: Compositions of ODT-SR of domperidone

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7
Domperidone MS	49.00	49.00	49.00	49.00	49.00	49.00	49.00
Microcrystalline Cellulose	86.75	__	__	43.37	43.37	28.91	28.91
Mannitol (Pearlitol)	---	86.75	---	43.37	---	57.83	---
Lactose	---	---	86.75	---	43.37	---	57.83
Crosslinked PVP (Polyplasdone XL-10)	12.00	12.00	12.00	12.00	12.00	12.00	12.00
Sodium saccharine	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Magnesium stearate	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Aerosil	0.75	0.75	0.75	0.75	0.75	0.75	0.75

Table III: Physical characterization of blends of ODT-SR ready for compression

Batch	Bulk Density (g/cm^3)	Tap Density (g/cm^3)	Percent Compress-ibility (%)	Angle of repose (º)	Hausner's ratio
F1	0.49	0.58	14.43	42.16	1.17
F2	0.51	0.57	11.73	23.00	1.13
F3	0.46	0.50	8.37	22.11	1.16
F4	0.47	0.54	11.47	24.02	1.12
F5	0.26	0.35	25.48	27.75	1.34
F6	0.51	0.60	15.04	25.42	1.17
F7	0.28	0.38	26.31	27.93	1.35

Table IV: Evaluation of ODT-SR of domperidone

Batch	Hardness (N)	Disintegration Time(sec)	Drug content (%)	Friability (%)
F1	35-40	42	95.30	0.24
F2	35-40	39	97.03	0.21
F3	35-40	44	97.00	0.17
F4	35-40	21	98.95	0.26
F5	35-40	32	98.89	0.14
F6	35-40	55	98.12	0.23
F7	35-40	46	98.83	0.16

Table V: Pharmacokinetic parameters of domperidone in rat after oral administration of conventional marketed tablet and developed ODT-SR (F-4)

| Parameters	Conventional Tablet (n=6) Mean±SD	ODT-SR (n=6) Mean±SD	P values
Cmax (μg/ml)	23.53±2.45	20.43±1.98	0.037
Tmax (h)	4±0.395	10±1.095	0.000
t½ (h)	1.07±0.056	3.01±0.0215	0.000
AUC_{0-24h} (μg.h/ml)	136.9 ±13.9	415.3 ±31.76	0.000
$AUMC_{0-24h}$ (μg.h²/ml)	528.7±43.5	4639±387	0.000
MRT (h)	3.86±0.1205	11.16±0.080	0.000

FIGURE LEGENDS

Figure No.	Figure Legends

Fig. 1   Chemical structure of domperidone

Fig.2   (a) Particle size distribution curve and (b) SEMof domperidone microspheres

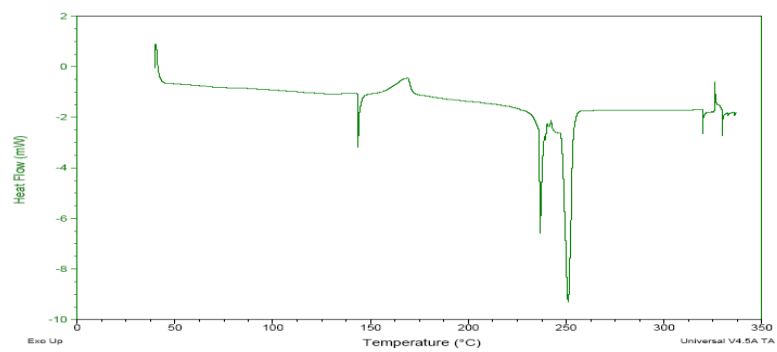Fig.3   Differential scanning thermograms of (a) Pure Domperidone

        (b) Ethyl cellulose and (c) Domperidone microsperes.

Fig.4   Comparative dissolution profile of optimized orodispersible sustained

        release tablet of domperidone (F4), marketed domperidone orodispersible

        (OC1) and marketed domperidone conventional tablet (OC2)

Fig.5   Plasma concentration Vs time plot of domperidone after oral

        administration of marketed orodispersible tablet and developed ODT-SR in rats
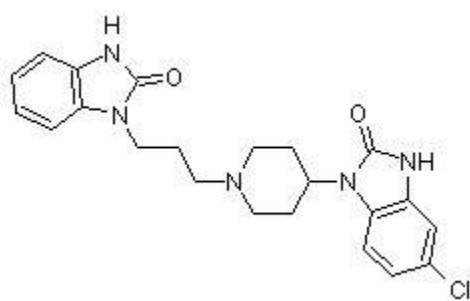
Figure 1: Chemical structure of domperidone
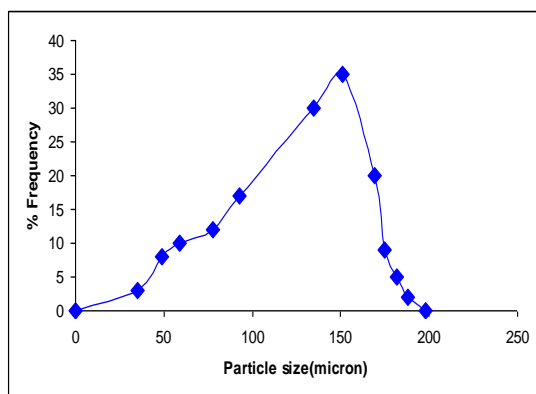
(a)   (b)

Figure 2: (a) Particle size distribution curve and (b) SEM of optimized domperidone microspheres
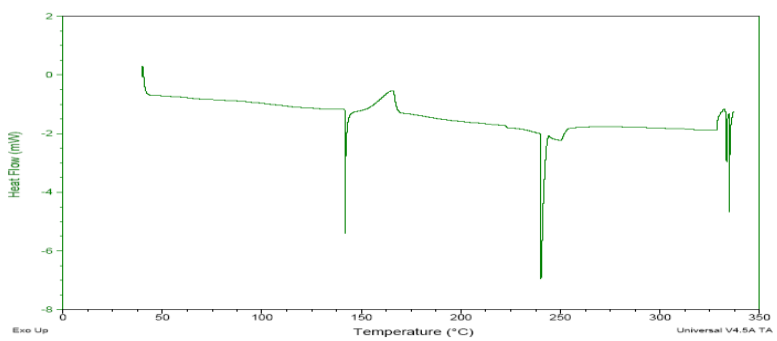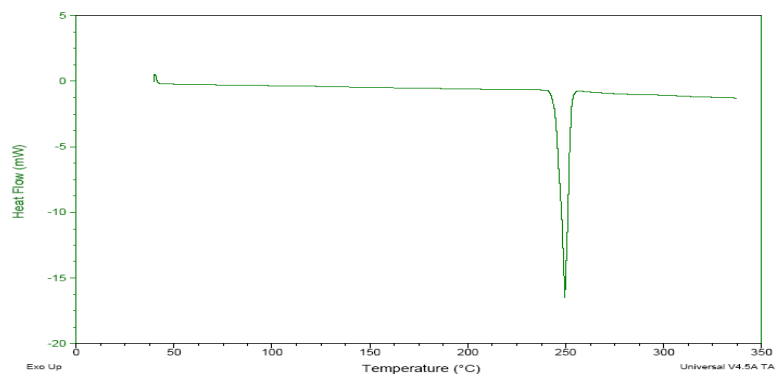
Figure 3: Differential scanning thermograms of (a) pure domperidone (b) ethyl cellulose and (c) domperidone microspheres
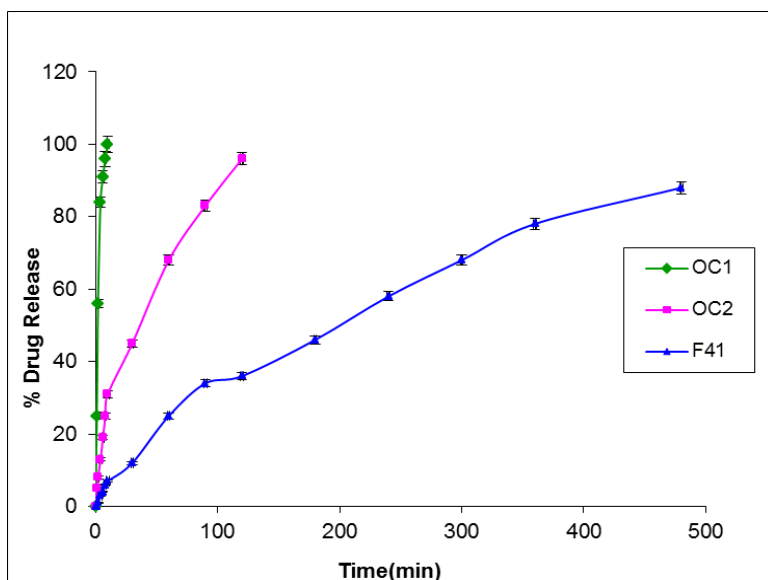
Figure 4: Comparative dissolution profile of optimized orodispersible sustained release tablet of domperidone (F4), marketed domperidone orodispersible tablet (OC1) and marketed domperidone conventional tablet (OC2)
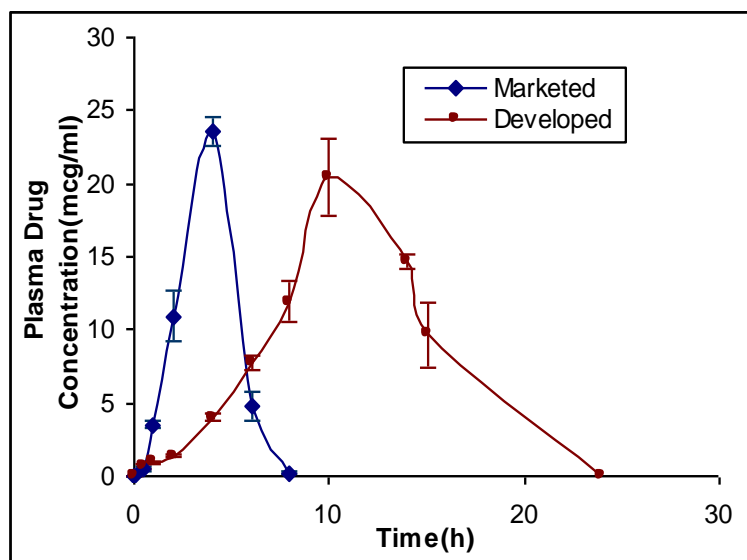

Figure 5: Plasma concentration vs. time plot of domperidone after oral administration of marketed conventional tablet and developed ODT-SR (F4) in rats