

Solubility and Dissolution Enhancement of Domperidone using 2-hydroxypropyl- β -cyclodextrin by Kneading Method

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Abstract

Objective: The objective of this study was solubility and dissolution enhancement of domperidone (DOM), and further they were formulated as mouth dissolving tablets (MDT). **Method:** DOM-solid dispersion (DOM-SD) was prepared using suitable complexing agent (2-hydroxypropyl- β -cyclodextrin) by kneading method; the solid dispersion prepared was further formulated into MDT by direct compression using super disintegrants (Kyron-T314, sodium starch glycolate, and *Plantago ovata* husk) in varying ratios. The prepared SDs were evaluated on Fourier transform infrared (FT-IR), percent yield, percent drug content (DC), saturation solubility, phase solubility, *in vitro* release, pre- and post-compression test. **Results and Discussions:** Percent yield and DC of DOM-SD was $81.48 \pm 4.35\%$ to $95.31 \pm 3.01\%$ and $91.96 \pm 0.72\%$ and $99.28 \pm 0.23\%$, respectively, saturation solubility was at higher in DOM-SD as compared to DOM alone, FT-IR studies revealed no drug excipient interaction except DOM-2-hydroxypropyl- β -cyclodextrin (2-HP β CD) which was deliberate, formulation KF5 showed best *in vitro* dissolution for DOM-SD. Pre-compression parameters like supported formulation of MDT of DOM. Post-compression parameters such as thickness, hardness, weight variation, friability, percent DC, water absorption ratio, wetting time, disintegration time, and *in vitro* dissolution suggested effective improvement and prompt release in the simulated conditions. The selected formulation KF2 also showed good stability data at accelerated conditions. **Conclusion:** DOM-SD was prepared using 2HP β CD which effectively enhanced DOM solubility and dissolution; moreover an effective DOM-MD was also prepared for prompt relief from nausea and vomiting.

Key words: Dissolution, kneading method, mouth dissolving tablet, solid dispersion, solubility

INTRODUCTION

Poorly aqueous soluble drugs are usually characterized by a low bioavailability due to less absorption, which is a major concern of pharmaceutical industries worldwide. Attempts to improve the solubility of these drug candidates have been performed by various approaches.^[1] Among them, solid dispersion (SD) technique has attracted considerable interest as an efficient means of improving the dissolution rate, which increases the solubility of a range of poorly aqueous soluble drugs.^[2-4] Fast and immediate drug dissolution from SDs has been observed due to increased wettability, improved dispersibility of drug particles, and existence of the drug in amorphous form with improved solubility and absence of aggregation of drug particles using various hydrophilic carriers.^[1-4]

Domperidone (DOM) is described chemically as 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazole-1-yl) propyl]-4-piperidinyl]-1, 3-dihydro-2H-benzimidazole-2-one [Figure 1].

DOM is a poorly water soluble dopamine D2 antagonist and widely used as an antiemetic. It is a basic, lipophilic BCS class II drug (poor solubility and high permeability).^[5,6] The elimination half-life is 5-7 h and protein binding of DOM is

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Received: 02-11-2016

Revised: 24-05-2017

Accepted: 12-06-2017

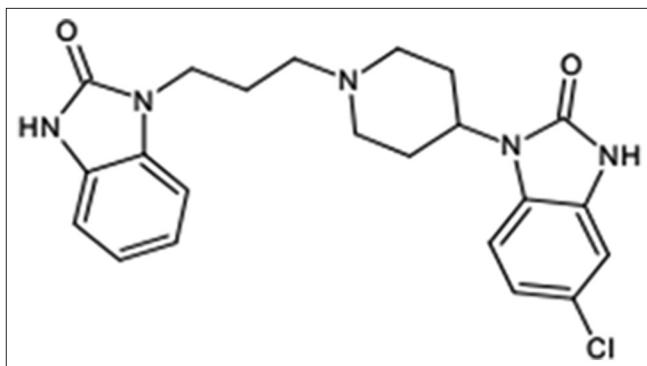


Figure 1: Structure of domperidone

91-93%. Although DOM is a weak base with good solubility in acidic pH, at alkaline pH, its solubility is significantly reduced.^[6,7]

Cyclodextrins (CDs) are powerful carriers for improving aqueous solubility through inclusion complexes. However, the complexation efficiency of CDs is low, and consequently, a significant amount of CDs are frequently needed to solubilize small amount of a water-insoluble drug.^[8-11]

The very low aqueous solubility and poor dissolution of DOM can cause formulation problems and limit its therapeutic application by delaying the rate of absorption and the onset of action.^[9,12] Therefore, improvements in solubility and/or dissolution rate of DOM may be achieved through the preparation of SDs. In the literature, various SDs of DOM are reported for improving the dissolution of DOM using various carriers such as polyvinyl pyrrolidone K 25 (PVP K 25),^[6] polyethylene glycol 4000 (PEG 4000),^[6] and PEG 6000.^[13]

Therefore, 2-hydroxypropyl- β -cyclodextrin (2HP β CD) as the suitable carrier for the preparation of SD was used in the present investigation. Hence, the aim of the present investigation is to prepare and characterize DOM SD using 2HP β CD as carrier for improvements of solubility and/or dissolution of poor aqueous soluble drug, DOM. Furthermore, attempt has been made to formulate DOM-mouth dissolving tablets (DOM-MDT) using super disintegrants.

MATERIALS AND METHODS

Materials

DOM was obtained as a gift sample from Souvenir Chemical, Mumbai, India. 2HP β CD was purchased from the Hi-media Laboratories, Mumbai, India. Kyron T-314 was a gift sample from the Corel Pharma Chem., Gujarat, India. Avicel pH 101 was purchased from the Fluka Analytica. Aerosil 200, magnesium stearate and Stearic acid were purchased from Central Drug House (P) Ltd, India. *Plantago ovata* Husk was purchased from the local market of Bareilly. All other reagents used were of A.R. grade.

Preparation of physical mixtures

To prepare physical mixtures of DOM and 2HP β CD (carrier) with different ratios (1:2, 1:4, 1:6, 1:8, and 1:10), the calculated amounts of drug and carriers were weighed and passed through sieve no 60 in a glass mortar by mixing for 10 min.^[14]

Preparation of DOM SDs using 2-HP β CD

SDs of DOM were prepared by kneading method using 2-HP β CD as carrier in 1:2, 1:4, 1:6, 1:8, and 1:10 ratios, respectively. In this method required amount of DOM and 2-HP β CD was taken and transferred into a mortar pestle. The mixture was size reduced by continuous stirring with pestle. Distilled water was added to the above physical mixture and continuously stirred until the slurry mass was formed. Slurry mass was collected and dried in hot air oven at 50°C. The dried mass was stored in desiccators until constant mass was obtained, crushed, and passed through sieve no. 60.^[14,15]

Fourier transform infrared (FT-IR) spectroscopy

Physicochemical characterization was performed using FT-IR spectroscopy. For this purpose, samples were reduced to powder and analyzed as KBr pellets by using an FT-IR spectrometer (Shimadzu-8400S, Japan).^[16] The samples were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:1, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press (Specac Atlas). The scanning range was 400-4700 cm⁻¹.

Determination of percent yield

The percent yield of DOM SDs was determined using the following formula:^[16]

$$\text{Percent yield} = \frac{\text{Weight of prepared solid dispersion}}{\text{Weight of drug + carriers}} \times 100$$

Drug content (DC)

Amount of SD equivalent to 10 mg of DOM was weighed accurately and dissolved in 10 ml of methanol. The volume was made up to the mark with methanol. The solution was suitably diluted with methanol and spectrophotometrically assayed for DC at 284 nm using the following formula:^[17,18]

$$\text{Percent DC} = \frac{\text{Concentration of drug released in medium}}{\text{Labeled claim}} \times 100$$

Saturation solubility

The solubility of SDs was determined using a 24 h shake flask method. Equivalent amount of SDs were weighted and

transfer in volumetric flask and added 10 ml phosphate buffer pH 6.8. After 24 h, the samples with sufficient dilutions were analyzed spectrophotometrically.^[19]

Phase solubility studies

Solubility studies were performed according to the method described by Higuchi and Connors.^[4] An excess amount of DOM was placed into a 25 mL glass flask containing different concentrations of 2HP β CD s in 20 mL distilled water. All flasks were closed with stopper and covered with cellophane membrane to avoid solvent loss, and the contents were shaken at 37°C for 72 h on rotary flask shaker (Remi RS-24 BL). After attainment of equilibrium, the content of each flask was then filtered through a Whatman filter paper no 42. The filtrate was diluted and assayed spectrophotometrically (Labindia UV-3200) for DOM content at 284 nm. All solubility measurements were performed in triplicate.^[20]

In vitro drug release

Dissolution experiments are performed in triplicate with a dissolution tester (Electrolab EDT-08LX USP II) in phosphate buffer pH 6.8 at 37 \pm 5°C using the paddle method at a rotation speed of 50 rpm. Powdered samples of each preparation equivalent to 10 mg of DOM were added to the dissolution medium (phosphate buffer pH 6.8). At appropriate time intervals, 5 ml of the mixture was withdrawn and filtered. The initial volume was replenished by adding 5 ml of fresh dissolution medium. The withdrawn samples were assayed for drug release at a wavelength 284 nm.^[19,20]

Preparation of DOM-MDT

Direct compression method

Different DOM-MDT were prepared according to the proportions given in Table 1. Avicel pH 101, superdisintegrants (Kyron T-314, Sodium Starch Glycolate SSG, and *P. ovata* husk) were passed through 60 # (250 μ m) before

use. Powdered 1:10 SD, containing amount equivalent to 88.5 mg DOM, was mixed with the other excipients were passed through a screen (60 mesh) before mixing and compressed on a single punch tablet machine (Coslab-01LX). The tablet weight was adjusted to ~300 mg.^[20-24]

Characterization of precompressed powder blend

Bulk density

The bulk density value includes the volume of all the pores within the sample. Accurately, weighted quantities of powder (M) were transferred into measuring cylinder, and initial volumes (V) were measured. The bulk density was calculated using the following formula:^[25]

$$\text{Bulk density} = \frac{\text{Weight of the sample}}{\text{Volume of the sample}}$$

Tapped density

The tapped value, or absolute density, of a sample excludes the volume of the pores and voids within the sample. Accurately, weighted quantities of powders (M) were transferred into measuring cylinder. The cylinders were then allowed to tap on to a bulk density apparatus for 100 times. The height of tapped powders were measured (V), then the tapped density was calculated using the following formula:^[26]

$$\text{Tapped density} = \frac{\text{Weight of the sample}}{\text{Volume of the sample}}$$

Carr's index and Hausner's ratio

The Carr's index and the Hausner's ratio were determined by measuring both the bulk density and tapped density of the powder. The Carr's and Hausner's ratio were calculated as follows:^[27]

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

Table 1: Formulation of DOM-MDT

Ingredients	KF1	KF2	KF3	KF4	KF5	KF6
SD complex	88.5	88.5	88.5	88.5	88.5	88.5
Kyron T-314	24	30	-	-	-	-
SSG	-	-	24	30	-	-
<i>Plantago ovata</i> husk	-	-	-	-	24	30
Avicel pH 101	178.5	172.5	178.5	172.5	178.5	172.5
Magnesium stearate	3	3	3	3	3	3
Stearic acid	3	3	3	3	3	3
Aerosil-200	3	3	3	3	3	3
Total weight	300	300	300	300	300	300

DOM-MDT: Domperidone-mouth dissolving tablets, SD: Solid dispersion, SSG: Sodium starch glycolate

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

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose (θ).

Angle of repose is defined as the maximum angle possible between the surface of a pile powder and horizontal plane.

The angle of repose of powder was determined by fixed funnel method to access the flow property of powders. The diameter of the powder cone (d) and the height (h) of the pile were noted. From the diameter, radius (r) was calculated. The angle of repose (θ) was calculated by using following formula:^[28,29]

$$\theta = \tan^{-1} \frac{h}{r}$$

Characterization of DOM-MDT

Uniformity of weight

The test was carried out according to the Indian pharmacopoeia. 20 tablets, from each formula, were individually weighed and the mean of tablet weights was calculated. Results are presented as mean value \pm standard deviation (SD).^[30,31]

Percent friability

About 20 tablets, from each formulation, were accurately weighed (W1) and placed in the drum of Friabilator (Coslab). The tablets were rotated at 25 rpm for 4 min and then removed, dedusted and accurately re-weighed (W2). The percentage loss in weight was calculated and taken as a measure of friability.^[32] The friability (F%) is given by the formula:

$$F(\%) = \frac{W1 - W2}{W1} \times 100$$

Weight variation

Every individual tablet in a batch should be in uniform weight and weight variation in within permissible limits. Weight control is based on a sample of 20 tablets. Determinations were made in triplicate.^[32]

Tablet thickness

Ten tablets from each formulation were taken randomly, and their thickness was measured with a Vernier Caliper.^[32]

Hardness

The hardness of the tablets was determined by diametric compression using a hardness testing apparatus (Pfizer's type). A tablet hardness of about 4-5 kg/cm² is considered adequate for mechanical stability. Determinations were made in triplicate.^[32]

In vitro disintegration time

One tablet from each formulation was placed in USP tablet disintegration apparatus without disk, containing 900 ml of pH 6.8 phosphate buffer at $37 \pm 0.5^\circ \text{C}$, and the time required for complete disintegration was determined.^[29]

Wetting time

Five circular tissue papers of 10 cm diameter were placed in a Petri dish with a 10 cm diameter. 10 ml of water at $37 \pm 0.5^\circ \text{C}$ containing eosin, a water-soluble dye, was added to the Petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time.^[29,33]

Water absorption ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio R was determined using following equation:^[29-35]

$$R = \frac{W_a - W_b}{W_a} \times 100$$

Where, W_a =Weight of tablet after water absorption,
 W_b =Weight of tablet before water absorption.

In vitro drug release studies

Drug release studies of the prepared DOM-MDT with either of semi synthetic or from natural super disintegrants were performed, in triplicate, in a USP Dissolution Apparatus II (Paddle type) (Electro lab EDT-08LX, India). The dissolution test was performed using phosphate buffer pH 6.8 at $37 \pm 0.5^\circ \text{C}$. The speed of rotation of paddle was set at 50 rpm. Aliquots of 1 mL were withdrawn from the dissolution apparatus at different time intervals and filtered through a cellulose acetate membrane (0.45 μm), and fresh dissolution medium was replenished immediately.

Absorbance of solution was checked by ultraviolet spectrophotometer (Labindia-3200) at a wavelength of 284 nm, and drug release was determined.^[32]

Accelerated stability studies

Stability studies were carried out on best formulation. The tablets were stored at 40°C and 75% RH for duration of 3 months. After every 1 month, samples were withdrawn and tested for various parameters such as hardness, DC, and *in vitro* drug release.^[32]

RESULTS AND DISCUSSION

Percent yield and DC

Various DOM SD using 2-HP β CD, at different ratios (1:2, 1:4, 1:6, 1:8, 1:10) were prepared by kneading method to increase the solubility and/or dissolution of poorly aqueous soluble drug, DOM. The percent yield of various DOM SD was found to be within the range of 81.48 \pm 4.35% to 95.31 \pm 3.01% [Table 2].

The percentage DC of prepared DOM SD ranged from 91.96 \pm 0.72% and 99.28 \pm 0.23%, as reported in Table 2. The values indicated that DOM was uniformly distributed in all of the prepared SD formulations.

Saturation solubility

The saturation solubility of DOM (3.1 \pm 0.22), and various newly prepared DOM-SD, and their respective physical mixtures in phosphate buffer, pH 6.8 was measured. DOM-SD showed higher saturation solubility than their respective physical mixtures of drug and carrier [Figure 2]. This might be an indicative reason for an improvement of wetting of drug particles and localized solubilization by the water-soluble carrier.

Drug-excipient compatibility studies

FT-IR studies were conducted by taking Drug Polymer in the ratio 1:1 to ascertain the compatibility between DOM and 2HP β CD, DOM + Kyron-T 314, DOM+SSG, DOM + *Plantago ovata* husk. The characteristic peaks of drug such as of N=C Stretching (1488.15 cm⁻¹), CH stretching symmetric (2819.09 cm⁻¹, 2932.89 cm⁻¹), N-C peaks (1694.54 cm⁻¹, 1693.57 cm⁻¹), C-O peaks (1023.28 cm⁻¹, 1033.89 cm⁻¹), and other sharp peaks at 608.57, 730.09 cm⁻¹ appeared for the drug and carrier shown in Figure 3.

In vitro dissolution study

The *in vitro* dissolution profiles of the drug (DOM), various SDs using 2-HP β CD in phosphate buffer (pH = 6.8) for 45 min are shown in Figure 4. All of the SD samples showed improved dissolution of DOM over pure DOM. The enhancement of dissolution is mainly attributed to increased

Table 2: Percentage yield and percent DC of DOM-SD

Formulations	Percentage practical yield	Percentage DC
K1	82.22 \pm 3.30	92.15 \pm 0.01
K2	81.48 \pm 4.35	91.96 \pm 0.72
K3	86.99 \pm 3.93	93.34 \pm 1.72
K4	92.06 \pm 4.33	96.28 \pm 1.19
K5	95.31 \pm 3.01	99.28 \pm 0.23

Mean \pm SD, *n*=3, DOM-SD: Domperidone-solid dispersion, DC: Drug content

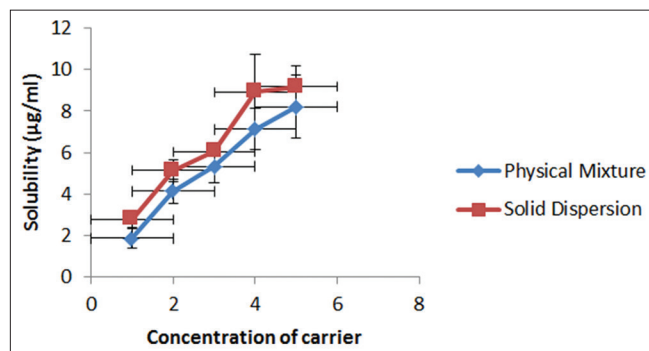


Figure 2: Saturation solubility of domperidone

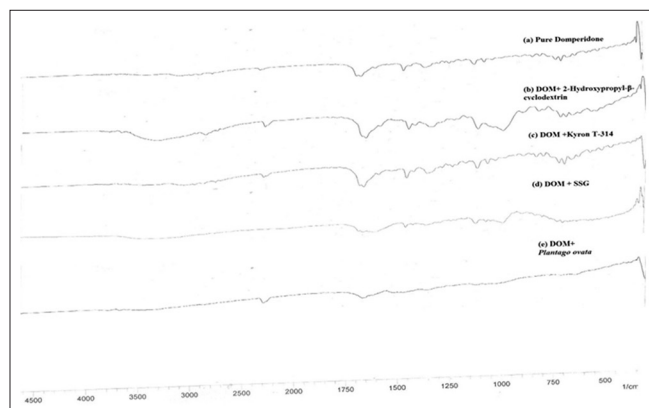


Figure 3: Fourier transform infrared spectra (a) pure domperidone (DOM), (b) DOM + 2-hydroxypropyl- β -cyclodextrin, (c) DOM + Kyron-T 314, (d) DOM + sodium starch glycolate, (e) DOM + *Plantago ovata*

surface area of drug exposed to large carrier molecules, increased wettability, and accordingly solubility due to polar effect of sugars containing polar groups.^[1] This also may be attributed to the higher hydrophilic sugar carriers, which can reduce the interfacial tension between the poorly aqueous soluble drug and the dissolution medium.

Phase solubility study

Phase solubility studies were carried out for assessment of the affinity between 2-HP β CD and drug molecule in water before preparing inclusion complex. The phase solubility

diagram for the complex formation of DOM with 2-HP β CD, Figure 5; illustrates linear increase of aqueous solubility of the drug ($R^2 = 0.9948$) as the concentration of 2-HP β CD increased over the entire concentration range studied and can be classified as A_p -type (the formation of soluble complexes containing more than one molecule of ligand leads to positive deviation from linearity) following the Higuchi and Connors classification. The linear correlation coefficient of DOM-2-HP β CD with a slope smaller than 1 indicated the increase in solubility was due to the formation of 1:1 water soluble complex in solution with respect to 2-HP β CD concentrations.

Evaluations of precompressed blend

The blend of all the batches was evaluated for parameters like angle of repose and was found to be between 29.7 and 32.0. Bulk density was found to be between 0.392 and 0.510 (gm/cc) and tapped density between 0.419 and 0.609 (gm/cc). Carr's Index was found to be in between 12.16 – 14.77, Hausner's ratio ranged between 1.12 and 1.17. All the formulations showed good blend properties for direct compression technology as shown in Table 3.

Evaluation of MDTs

Results for hardness, friability, content uniformity, and disintegration time are indicated in Table 4 and were found to be well within the limits. The hardness of the tablets was found to be between 3.23 and 4.95 kg/cm², and friability was found to be below 1% which indicated good mechanical resistance. The DC was found to be in the range 98.77 ± 1.00 to 99.93 ± 1.01 shown in Table 4.

In vitro drug release

The *in vitro* drug release studies were performed on the formulations prepared using either natural or semi-synthetic super disintegrants, drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved. The percent drug release from the selected formulations (KF2, KF4) MDTs of DOM using Kyron T-314, SSG as super disintegrants presented 99.25% and 96.85% release in 15 min Figure 6. Almost every formulation exhibited more than 90% drug release in 15 min, this can be attributed to the fact that the drug dispersion in the carrier made commendable increment in the wettability thereby producing similar dissolution profile of the MDTs, the only difference was in their disintegration time which in turn governs the dissolution time of the formulation.

Stability study

The stability of the selected formulation KF2 was known by performing stability studies for 3 months at accelerated conditions of $40^\circ\text{C} \pm 75\% \text{ RH}$. The formulation was found

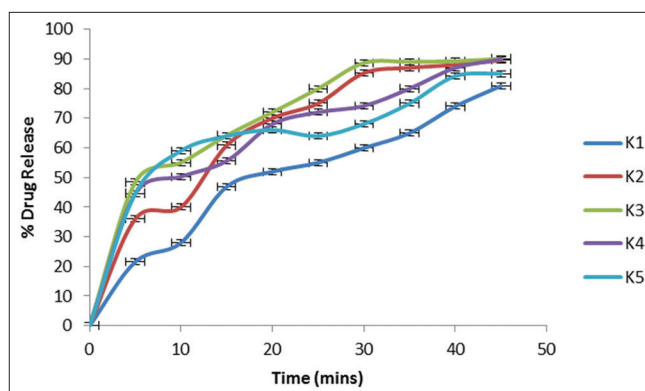


Figure 4: Drug release profile of solid dispersion of domperidone by kneading method

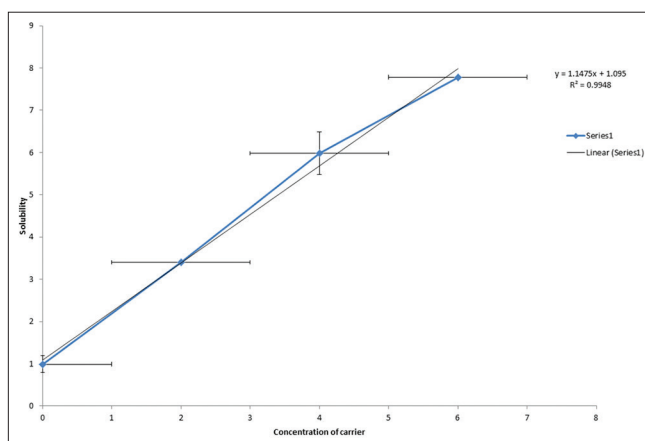


Figure 5: Phase solubility study

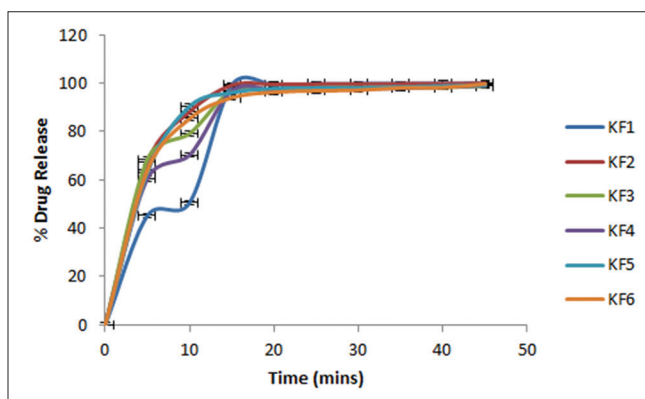


Figure 6: Drug release profile of domperidone-mouth dissolving tablets by kneading method

to be stable, with insignificant change in the hardness, disintegration time, and *in vitro* drug release pattern the data have been given in Table 5.

CONCLUSION

DOM SDs using 2-HP β CD as carrier was successfully prepared by kneading method. FT-IR spectroscopy revealed

Table 3: Precompression parameters of powdered blend of different formulations

Formulations	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
KF1	0.392	0.442	11.30	1.12	30.2°
KF2	0.461	0.520	11.30	1.12	29.7°
KF3	0.490	0.419	14.40	1.16	30.0°
KF4	0.410	0.463	11.40	1.12	29.9°
KF5	0.449	0.519	13.40	1.15	30.3°
KF6	0.403	0.469	14.00	1.16	30.4°

Table 4: *In vitro* evaluation data of DOM-MDT

Formulations	Thickness (mm)*	Hardness (kg/cm ³)*	Weight variation (mg)*	Friability (% w/w)	DC (%)*	Water absorption ratio (%)	WT (s)	DT (s)
KF1	4.65±0.21	2.75±0.49	300.1±4.73	0.013	99.2±1.05	80.2±0.10	49	47
KF2	4.40±0.20	3.45±0.07	301.6±4.06	0.057	101.2±0.23	81.2±0.05	42	38
KF3	4.65±0.07	3.50±0.56	298.1±2.38	0.011	99.8±1.65	75.3 ±0.15	52	48
KF4	4.45±0.07	3.45±0.07	302.1±2.91	0.073	102.1±0.27	76.2 ± 0.11	49	45
KF5	4.50±0.42	3.95±0.21	301.9±4.34	0.021	101.07±1.79	72.1 ± 0.30	55	53
KF6	4.45±0.35	3.90±0.42	303.7±3.86	0.017	99.33±0.63	71.5 ± 0.20	58	55

DOM-MDT: Domperidone-mouth dissolving tablets, DC: Drug content, WT: Wetting time, DT: Disintegration time, Mean±SD, n=3

Table 5: Stability study data for optimized formulation

Parameters	Time in months			
	Formulation KF2			
	Initial	1 st month	2 nd month	3 rd month
Hardness (kg/cm ²)	3.45	3.68	3.70	3.71
Disintegration time (s)	38	39	39	40
DC (%)	101.29	101.00	100.55	99.88
Drug release (%)	99.25	99.12	98.88	98.76

DC: Drug content

the possibility of intermolecular hydrogen bonding in various SDs. The saturation solubility and *in vitro* dissolution studies showed a remarkable increase in both the solubility and dissolution of DOM-SD (3-fold) using 2HPβCD as compared with pure DOM. As demonstrated by FT-IR studies, the amorphization of DOM offered an explanation of better dissolution rate from its SD. From the present study, it can be concluded that the super disintegrants and carrier 2HPβCD played an important role to decrease disintegration time and to enhance the dissolution rate.

ACKNOWLEDGMENT

The authors are thankful to Souvenir Chemical, Mumbai, India, for provided the gift sample of DOM and also thankful to the management, Invertis Institute of Pharmacy, Invertis University, Bareilly for providing the financial and instrumental facility for the entire duration of research work.

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Source of Support: Nil. **Conflict of Interest:** None declared.