

FORMULATION AND EVALUATION OF MELT-IN-MOUTH TABLETS OF DOMPERIDONE CONTAINING MULTICOMPONENT INCLUSION COMPLEX

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ABSTRACT

The purpose of this study was to formulate melt in mouth tablets of domperidone containing multicomponent inclusion complex. Multicomponent inclusion complex of domperidone (DOM) was prepared with β -cyclodextrin (β CD), polyvinyl pyrrolidone (PVP) K40 and citric acid to improve the solubility and dissolution rate of domperidone. Tablets were prepared by using three superdisintegrants croscopolvidone, sodium starch glycolate and croscarmellose sodium and with direct compression method. Accelerated stability studies for tablets were carried out as per ICH guidelines revealed that the tablets were stable.

Keywords: Domperidone, Melt in mouth tablets, Multicomponent inclusion complex, Solubility.

INTRODUCTION

Today, the innovative delivery systems such as 'melt in mouth' or 'mouth dissolving tablets' have gained attention of research scientists due to the advantages that these systems provide. Melt in mouth tablets can be administered without water anywhere and at anytime. They are suitable for geriatric and pediatric patients who find it difficult to swallow solid oral dosage forms. They are also most suitable for drugs that undergo extensive first pass metabolism. The benefits, in terms of patient compliance, rapid onset of action as the drug goes directly into systemic circulation and good stability, make these tablets popular as a dosage form of choice in the current market ¹.

Domperidone (DOM) is a poorly water soluble dopamine D2 antagonist and widely used as an antiemetic. It is a basic, lipophilic BCS Class II drug. It possesses very poor oral bioavailability and shows significant first pass metabolism. An intravenous administration of domperidone causes cardiac arrest ². Thus, there is need to improve bioavailability of DOM by increasing its aqueous solubility and overcoming the first pass metabolism if it is to be delivered by oral route ³. This encouraged the authors to study the improvement of solubility of DOM by preparing multicomponent inclusion complex with β -CD, water soluble polymer and hydroxy acid (separately or in combination) and formulating the mouth dissolving tablets of the prepared complex.

Poorly water-soluble drugs provide challenges for the oral formulation since their water-solubility and rate of dissolution are a limiting factors for their absorption and biological availability ⁴. Thus there is a need to improve their solubility so as to increase their oral bioavailability. Cyclodextrins are powerful carriers for improving aqueous solubility through inclusion complexes ⁵. However the complexation efficiency of CDs is low and consequently a significant amount of CD is frequently needed to solubilize small amount of a water insoluble drug. The drug solubility in the presence of CD can be dramatically improved by addition of suitable components such as hydroxy acids and water soluble polymers. Multicomponent inclusion complex of a poorly soluble basic drug, CD, water soluble polymer and hydroxy acid can enhance the solubility of drug multifold ^{6,7}.

MATERIALS AND METHODS

Domperidone was kindly gifted by FDC, Mumbai, Maharashtra, India. β -cyclodextrin was available from commercial source. All other chemicals used in the study were of analytical grade.

Preparation of multicomponent inclusion complexes and physical mixtures

The DOM/ β -CD binary complex (1:1), DOM/ β -CD/ citric acid ternary complex (1:1:0.5), DOM/ β -CD/ PVP K40 ternary complex

(1:1:14%w/w) and DOM/ β -CD/ citric acid/PVP K40 quaternary complex (1:1:0.5:14%w/w) were prepared by kneading method. Accurately weighed quantity of β -CD was mixed with sufficient quantity of water to obtain a smooth and homogenous paste. Weighed quantity of DOM alone (for binary complex) or along with citric acid and/or PVP K40 (for ternary and quaternary complex) was added slowly by grinding. The mixture was ground for one hour. Finally the paste was dried in hot air oven at 40°C for 48 hrs. The dried complex was powdered and passed through sieve no. 100 and stored in air tight container till further use. The physical mixtures containing same composition as that of respective complexes were also prepared for comparative study ⁸.

In-vitro dissolution studies for complexes

Dissolution studies for DOM inclusion complexes and physical mixtures were performed in 900 ml phosphate buffer pH 6.8 at stirring speed 50 rpm and temperature 37°C \pm 0.5 °C. Powder sample equivalent to 10 mg DOM was tested in phosphate buffer pH 6.8. At fixed time intervals, samples were collected, filtered by using a 0.45 μ m Millipore filter and spectrophotometrically analyzed at 284 nm.

Formulation of melt in mouth tablets of domperidone

Tablets were prepared with optimized multicomponent inclusion complex of DOM. Preformulation studies were conducted prior to compression of tablets. Tablets containing multicomponent inclusion complex (equivalent to 10 mg of DOM) were prepared by direct compression using a 12-station, tablet machine (M/s Rimek Tableting Machine, mini press-II MT, Karnawati Engineering Ltd, India) using a concave 7 mm die and punch set. The excipients such as superdisintegrants (croscopolvidone, sodium starch glycolate, croscarmellose sodium), microcrystalline cellulose (Avicel pH 102), vanilla flavor, sodium saccharin and magnesium stearate were added as per the composition given in Table 1. The prepared tablets were evaluated for hardness, friability, content uniformity, disintegration time, wetting time and *in vitro* dissolution.

Evaluation of melt in mouth tablets

Friability testing

Twenty tablets from each formulation were evaluated for uniformity in tablet weight according to Indian Pharmacopoeia (2007) by using Roche friabilator. Hardness was determined using a Monsanto type hardness tester.

Disintegration time

Disintegration time for mouth dissolving tablets was determined according to USP30, in 900 ml phosphate buffer (pH 6.8) at 37 \pm 2°C using USP disintegration apparatus.

Wetting time

A piece of tissue paper folded twice was placed in a petri dish (internal diameter -5cm) containing 6ml of phosphate buffer solution (pH 6.8). Tablet was placed on the paper and the time taken for complete wetting was noted ⁹.

In-vitro dissolution studies

In vitro dissolution study of melt in mouth tablets was performed in phosphate buffer pH 6.8 (900ml) using USP type II (paddle) apparatus operated at 50 rpm for 16 minutes ($37 \pm 0.5^\circ\text{C}$)⁹.

Stability study

The accelerated stability study of prepared tablets was carried out in a stability chamber (Remi environmental test chamber, CHM 6S) as per ICH guidelines at $40^\circ\text{C}/75\% \text{RH}$ for up to 3 months. Samples

were evaluated for hardness, disintegration time, wetting time, drug content and dissolution studies.

RESULTS

In-vitro dissolution studies for complexes

Comparisons of dissolution patterns of pure DOM with various inclusion complexes and physical mixtures are shown in Fig. 1.

Preformulation studies

Preformulation studies for tablet blend are given in Table 2.

Evaluation of mouth dissolving tablets

After compression all the formulations are evaluated for friability, wetting time, drug content and disintegration time as shown in Table 3.

Table 1: Composition of different batches of tablets

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Optimized complex ~10mg Domperidone	44.38	44.38	44.38	44.38	44.38	44.38	44.38	44.38	44.38
Crosspovidone	3.5	5.5	7.5	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	3.5	5.5	7.5	-	-	-
Crosscarmellose	-	-	-	-	-	-	3.5	5.5	7.5
Avicel pH102	97.12	95.12	93.12	97.12	95.12	93.12	97.12	95.12	93.12
Vanilla flavor	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium saccharin	2	2	2	2	2	2	2	2	2
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

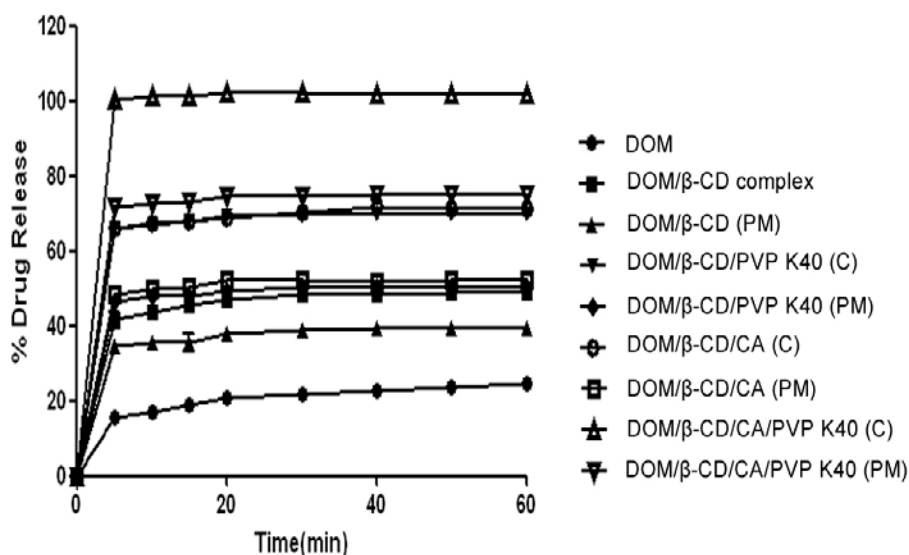


Fig. 1: Dissolution profile of DOM, inclusion complexes and physical mixtures.

[(C): Inclusion complex; (PM): Physical mixture; (CA): Citric acid]

Table 2: Preformulation studies of mouth dissolving tablet blend

Formulations	Angle of repose* \pm SD	Carr's index* \pm SD	Hausner's ratio* \pm SD
F1	24.13 \pm 1.01	15.84 \pm 1.43	1.19 \pm 0.01
F2	24.13 \pm 0.42	14.17 \pm 1.44	1.17 \pm 0.01
F3	25.37 \pm 0.74	14.03 \pm 1.51	1.16 \pm 0.02
F4	26.48 \pm 0.31	15.83 \pm 1.44	1.19 \pm 0.02
F5	26.58 \pm 0.39	17.50 \pm 0.00	1.21 \pm 0.00
F6	26.15 \pm 1.01	15.83 \pm 1.44	1.19 \pm 0.01
F7	24.41 \pm 0.43	14.91 \pm 1.52	1.18 \pm 0.02
F8	24.44 \pm 0.14	15.79 \pm 0.00	1.19 \pm 0.00
F9	24.10 \pm 0.78	15.00 \pm 0.00	1.18 \pm 0.00

* Mean of three readings; SD- Standard deviation.

Table 3: Evaluation of prepared formulations containing quaternary inclusion complex

Formulations	Friability (%)	Wetting time* (Sec) \pm SD	Drug content* (%) \pm SD	Disintegration Time* (sec) \pm SD
F1	0.42	71.33 \pm 1.15	99.10 \pm 1.53	60.66 \pm 1.15
F2	0.35	69.67 \pm 2.08	98.54 \pm 1.48	63 \pm 1
F3	0.54	54 \pm 1.73	99.32 \pm 0.81	54.66 \pm 0.57
F4	0.83	178.33 \pm 2.52	98.25 \pm 1	141 \pm 1.73
F5	0.76	133 \pm 1	98.15 \pm 1.16	108.66 \pm 1.15
F6	0.58	118.66 \pm 1.52	102.13 \pm 0.88	99 \pm 1
F7	0.68	52.66 \pm 0.57	99.86 \pm 1.63	43 \pm 2
F8	0.46	43.33 \pm 1.52	101.35 \pm 1.04	37.46 \pm 1.15
F9	0.49	42.81 \pm 2.30	99.78 \pm 0.86	36.66 \pm 1.52

*Mean of three readings; SD- Standard deviation.



Fig. 2: Disintegration time for optimized (F8) formulation

Disintegration time at 0 sec. Disintegration time at 37.46 sec.

In-vitro dissolution studies for prepared formulations

Dissolution profiles for prepared formulations are shown in Fig. 3.

Stability studies

Data of stability studies for optimized formulation (F8) is shown in Table 4. IR analysis of optimized inclusion complex and optimized F8 formulation before and after stability study is given in Fig. 4.

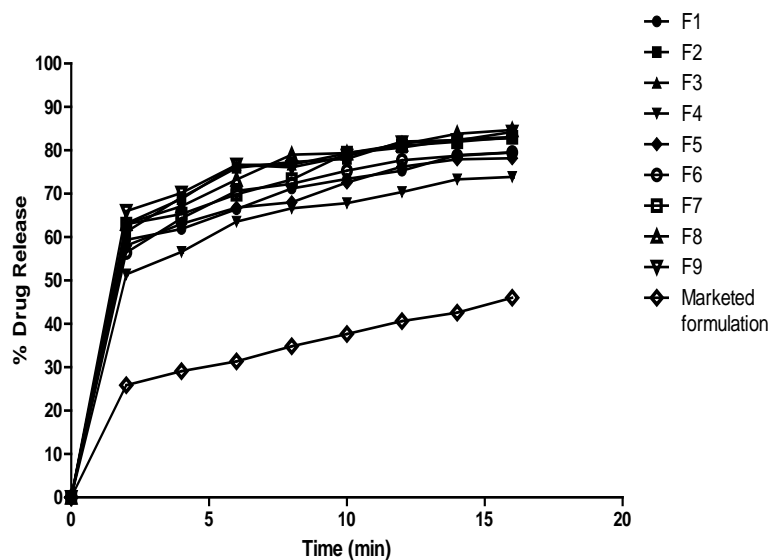


Fig. 3: In vitro dissolution profiles of prepared formulations

Table 4: Stability study data for optimized formulations containing quaternary (DOM/ β -CD/ citric acid/PVP K40) inclusion complex.

Test parameters	0 months	After 3 month	After 6 months
1. Disintegration time* (Sec) \pm SD	37.66 \pm 1.15	39.33 \pm 1.52	40.66 \pm 1.52
2. Wetting time* (sec)	42.33 \pm 1.52	44.66 \pm 1.52	45.66 \pm 3.05
3. Drug content* (%) \pm SD	101.37 \pm 0.68	99.23 \pm 0.97	98.10 \pm 0.52
4. Drug release* after 16 min (%) \pm SD	84.67 \pm 0.94	83.35 \pm 1.12	81.86 \pm 1.52

* Mean of three readings; SD- Standard deviation.

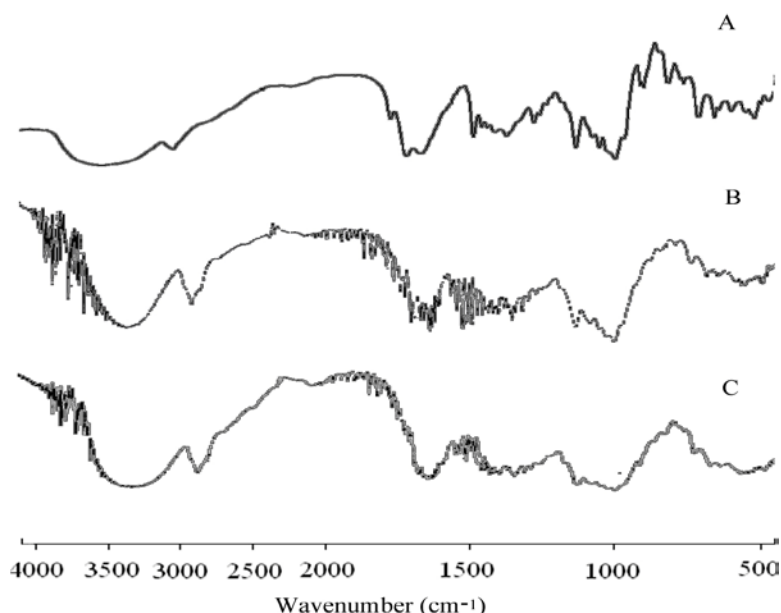


Fig. 4: IR analysis of optimized inclusion complex (DOM/ β -CD/citric acid/PVP K40) (A) and optimized F8 formulation before (B) and after (C) stability study

DISCUSSION

Fig.1 shows comparisons of dissolution patterns of pure DOM with various inclusion complexes and physical mixtures. The release rate profiles were expressed in percentage of drug released versus time. The (DOM/ β -CD/ citric acid/PVP K40) quaternary complex (1:1:0.5:14%w/w) showed higher dissolution rate as compared to ternary complex (DOM/ β -CD/ PVP K40), ternary complex (DOM/ β -CD/ citric acid), binary complex (DOM/ β -CD) and pure drug. Pure drug showed 18.88 % release whereas binary complex showed 47.71 % release within 5 min. The ternary inclusion complex containing PVP K40 (14%) showed 66.28% drug release within 5 min. The preliminary studies revealed that dissolution of DOM decreased after increasing polymer concentration above 14%. This may be due to formation of water insoluble inclusion complexes between polymer and several β -CD molecules ⁷.

The ternary inclusion complex with citric acid showed 66.36% release. The quaternary inclusion complex showed 100.66% release within 5 min which was significantly higher ($p < 0.05$) than physical mixtures and binary complex. The enhancement in the dissolution was due to formation of inclusion complexes in the solid state with reduction in the crystallinity of DOM, leading to increased hydrophilicity, higher wetting effect and increased contact between drug and the carrier. Therefore quaternary inclusion complex (DOM/ β -CD/ citric acid/PVP K40) was optimized. Tablets were prepared by using optimized complex with direct compression method.

As per given in Table 2, the angle of repose was found in the range of 24.10 to 26.58°. Carr's index of the prepared blends fall in the range of 14.03-17.50% and this is also supported by Hausner ratio values which were in the range of 1.16-1.21. Thus, the blend prepared for tablets possessed good flow properties and were suitable for direct compression.

All the formulations prepared by direct compression exhibited white color, convex shape and smooth surface. The friability, drug content, wetting time and disintegration time of prepared tablets are shown in Table 3. Hardness of tablets prepared by direct compression was between 3 and 4 kg/cm². The friability of all formulations was found to be less than 1%. Disintegration time is very important factor for mouth dissolving tablets. Rapid disintegration time assist swallowing of tablet and plays important role in drug absorption in buccal cavity which helps to increase bioavailability of drug. Disintegration time for prepared formulations was in the range of 35

sec to 140 sec. Cross carmellose sodium showed lower disintegration time than sodium starch glycolate and crosspovidone. Fig. 2 shows disintegration time for optimized (F8) formulation. Wetting time is used as an indicator for the ease of tablet disintegration in buccal cavity. Wetting time for all formulations were obtained in the range 43 sec to 180 sec. Different superdisintegrants showed different wetting time for tablets. Order for wetting time was cross carmellose sodium > crosspovidone > sodium starch glycolate¹⁰. The drug content of the prepared tablets was in the range of 99.12 to 102.13 %. The low values of standard deviation indicated uniform drug distribution in tablets.

In vitro dissolution studies for all 9 formulations were performed in phosphate buffer (pH 6.8). Dissolution profiles of all formulations are shown in Fig. 3. F8 formulation showed highest % drug release (84.67 % within 16 min). With reference to the type of superdisintegrant, the release rate was found to follow the order: cross carmellose sodium > crosspovidone > sodium starch glycolate. Dissolution process of tablet depends upon wetting followed by disintegration of the tablet. As the formulation containing cross carmellose sodium showed rapid wetting and disintegration, it ultimately led to high release rate. The release rate of all the formulations was found to be significantly higher ($p < 0.05$) than the marketed formulation indicating faster release of the prepared formulations. F8 formulation was optimized because it showed higher % drug release than all other formulations. F8 and F9 formulation denoted somewhat similar disintegration time, wetting time and % drug release. But F8 formulation was optimized because it has lower percentage of superdisintegrant.

There were no appreciable changes was observed in physical characteristics, hardness, disintegration time, wetting time, drug content and dissolution profile after 3 months and 6 months stability studies for optimized F8 formulation, stability studies data is given in Table 4.

IR spectra of DOM, optimized formulation F8 and F8 for stability testing are shown in Fig. 4 The pure drug showed characteristic absorption bands at N-H stretching at 3129.90 cm⁻¹, N-H bending at 1620.6 cm⁻¹ and C = O stretching at 1711.80 cm⁻¹, indicating the presence of -CONH group, asymmetric C-H stretching at 2943.10 cm⁻¹, symmetric C-H stretching at 2816.60 cm⁻¹, aromatic C-H stretching at 3015.70 cm⁻¹ The characteristic absorption band at 759.30 cm⁻¹ with strong stretching intensities may be attributed to presence of -C-Cl bond ¹¹. All the characteristic peaks of DOM are remaining intact in optimized formulation F8 and F8 for stability testing.

Therefore no any chemical interaction obtained between DOM and other components used for tablet preparation.

CONCLUSION

Melt in mouth tablets containing optimized multicomponent inclusion complex (DOM/ β -CD/ citric acid/PVP K40) of DOM were prepared by direct compression method. Optimized F8 formulation showed 84.67 % drug release within 16 min. In stability studies for optimized F8 formulation, there were no significant changes were recorded with respect to hardness, disintegration time, wetting time, drug content, percentage drug release and infra red spectroscopy over a period of six months, so F8 formulation was stable.

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