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Research Article

FORMULATION AND EVALUATION OF TASTE MASKED ORAL DISPERSIBLE TABLETS OF DOMPERIDONE USING SUBLIMATION METHOD

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ABSTRACT

Difficulty in swallowing (dysphagia) is common among all age groups, especially for geriatric and pediatric patients. Oral dispersible tablets (ODT) constitute an innovative dosage form that overcome the problems of swallowing and provides a quick onset of action. The aim of the present research was to prepare taste masked oral dispersible tablets by sublimation method and investigate the effects of super disintegrant (Kollidon CL) on the disintegration time as well as the percent release of a model drug from Kollidon 30, Ispaghula husk and Guar Gum based formulations. Domperidone, an anti-emetic drug was taken as the model drug for the study. A high porosity was achieved using camphor as volatilizing agent which allowed easy penetration of dissolution media followed by rapid release of drug. The granules and tablets were evaluated and found to be acceptable according to standard limits. *In vitro* release studies were performed using USP apparatus-II (paddle method) in 900ml of 0.1N HCl (pH 1.2) at 50rpm. The release mechanisms were explored and explained with different kinetic model. Kollidon CL was found to cause a rapid disintegration of ODTs within 24 to 39 seconds. The highest drug release was obtained from F-6 (88.19%) containing Ispaghula husk. Finally, the overall study indicate a proper balance between the rate retarding polymers and disintegrant having a drug release profile of ODT under the presence of a volatilizing agent showed an acceptable disintegration time with a percent of drug release.

Keywords: Domperidone, Oral dispersible tablets, Direct Compression, Kollidon CL, Sublimation method.

INTRODUCTION

Oral route of drug administration have wide acceptance, up to 50-60% of oral solid dosage forms are popular because of natural, uncomplicated, convenient, ease of administration, accurate dosage, self medication, pain avoidance and most importantly patient compliance. The most popular solid dosage forms being tablets and capsules, one important drawback of these dosage forms for patient is the difficulty to swallow [1]. Many patient groups such as the elderly, children, and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid-intake/diets, have difficulties swallowing these dosage forms. Those who are traveling or have little access to water are similarly affected [2,3,4]. Almost 50% of the population is affected by such problem, resulting in the high incidence of non compliance and ineffective therapy [5].

A constant focus on Novel Drug Delivery systems that offer greater patient compliance, effective dosage and minimal side effects has led to the development of oral dispersible tablets (ODT). To improve the quality of life and treatment compliances of such patients fast disintegrating or orally disintegrating tablets dosage form is a better alternative for oral medication [6]. ODTs undergo disaggregation in the mouth when in contact with the saliva in less than 60 seconds, preferably in less than 40 seconds, forming a suspension which is easy to swallow [7]. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is significantly greater than those observed from conventional tablet dosage form [8].

In the recent past, several new advanced technologies have been introduced for the formulation of (ODTs) like lyophilization [9], moulding [10], direct compression [11], cotton candy process[12], spray drying [13], sublimation [14], mass extrusion [15], nanonization [16] and quick dissolve film formation [17]. These techniques are based on the principles of increasing porosity and/or addition of superdisintegrants and water soluble excipients in the tablets. The formulations prepared from these techniques differ from each other on the basis of the factors like mechanical strength of final product, drug and dosage form stability, mouth feel, taste, rate of dissolution of the formulation in saliva, rate of absorption from saliva and overall drug bioavailability [18].

Domperidone (IUPAC name: 5-chloro-1-(1-[3-(2-oxo-2, 3-dihydro-1*H*-benzo[*d*]imidazol-1-yl) propyl] piperidin-4-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one) is selected as the model drug (Figure 1) which comes under anti-emetic class [19]. It can be used in patients with Parkinson's disease, because it does not cross the blood-brain barrier [20]. Domperidone has also been found effective in the treatment of gastroparesis and for pediatric gastro esophageal reflux (infant vomiting) [21]. Its usual dose is 10 mg twice daily [22]. Domperidone is optimized suits for preparation of ODT as it has longer half life and in case of vomiting it required quick release [23]. Again, It has been reported that Domperidone possess bitter taste hence the primary objective is to mask the bitter taste and further developing the drug into Oral dispersible tablets [24].

The purpose of this study was to develop taste masked orally disintegrating dosage form of a model drug, Domperidone by sublimation method using camphor as sublimating agent along with mannitol provided porous tablets that on administration rapidly disintegrated in the oral cavity, without the need of swallowing or intake of water and also rapid drug release rate. To achieve this goal, tablets were directly compressed with different polymers or binders (Kollidon 30, Ispaghula Husk and Guar Gum) against different concentrations of a superdisintegrant (Kollidon CL). The Disintegration time (DT), hardness and friability with *in vitro* drug release characteristics from the compressed tablets were also examined to establish the conditions of a successive ODT formulation.

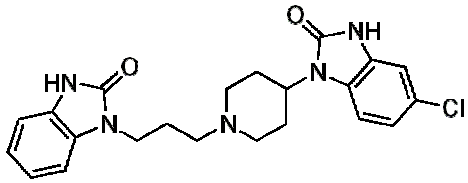

Fig. 1: Chemical structure of Domperidone

Investigations were performed to understand the effect of disintegrating agents (types and amounts) upon the disintegration time (DT) as well as the percent release of Domperidone from the ODT formulations. The release rate, extent and mechanisms were found to be governed by the type of binder and disintegrant contents. The release mechanisms were explored and explained with zero order, Higuchi and Korsmeyer equations. The impact of formulation variables that means polymer types, disintegrating agent contents and type of disintegrants upon release rate, extent and mechanisms were also investigated which provide important information regarding the drug release rate from the ODT formulations.

MATERIALS AND METHODS

Active Drug (Domperidone), binders (Kollidon 30, Ispaghula Husk and Guar Gum), superdisintegrants (Kollidon CL) was collected from Eskayef Pharmaceuticals Limited, Bangladesh.

Other Excipients

Camphor, Aspartame and Mannitol were gift from Eskayef Pharmaceuticals Limited. Moreover, Magnesium Stearate, Microcrystalline Cellulose (Avicel PH-101), Talc, Cab-o-Sil ware collected from research laboratory.

Solvents and Reagents

Potassium Dihydrogen Ortho Phosphate (Techno Pharma, Bangladesh), Sodium Hydroxide (Merck, Germany). All other reagents employed were of analytical or pharmaceutical grade.

Equipments

UV Visible Spectrophotometer (HACH, model-DR/4000u); Dissolution Tester (PHARMA TEST, model-DT 70); Disintegration Tester (PHARMA TEST, D-63512); Hardness Tester (PHARMA TEST, Germany); Friability Tester (PHARMA TEST, Germany); Electric Balance (Denver Instrument, model-M-310); Digital pH Meter (LIDA Instrument, model-PHS-25); Single Punch Tablet Press (Single punch machine, India).

Preparation of Orally Disintegrating Tablets

Drug, binder, superdisintegrant and other excipients were weighed separately for 100 tablets per formulation as per proposed formulations. The proposed formulations were coded as F-1, F-2, F-3, F-4, F-5, F-6, F-7 and F-8. The amounts of drug and excipients are expressed in mg (milligram) unit. At first the binder, superdisintegrant, camphor and aspartame were mixed and passed through sieve no. 40. Then Domperidone (API) was added and mixed properly within 10-15 minutes and sieved again. Avicel (MCC) and Mannitol were added and mixed properly for 5 minutes. Finally, Mg-stearate, Talc, Cab-o-Sil and Orange flavor were also added to the mixture. Blended mass was taken in the hopper and then die and punch were adjusted to get the desired weight of the tablet (300 mg). Tablets were prepared using flat face round 11 mm diameter punch on Single Punch Tablet Press (Single punch machine, India).

Direct compression process was selected for these formulations, because porous nature is more in direct compression blend than wet granulation blend. So, it will give faster disintegration. After compression the tablets were subjected to sublimation at 60^0 C for 6 hrs in vacuum oven. A schematic representation of tablet preparation is shown in Figure 2 and the types and amounts of polymers used in different formulation are shown in Table 1.

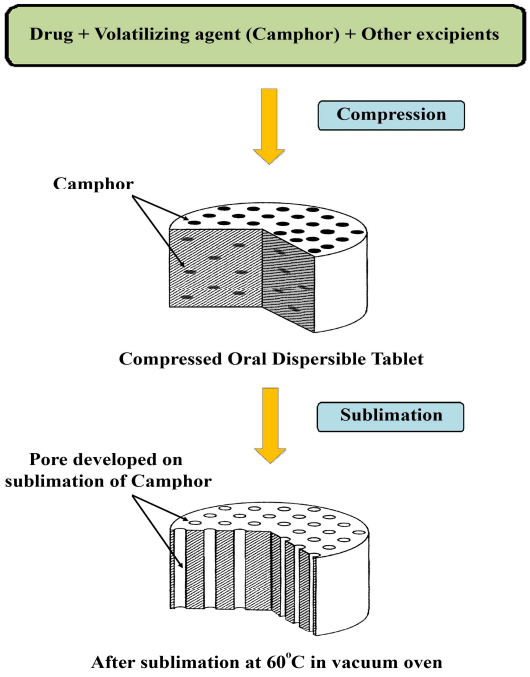

Fig. 2: Schematic illustration of the preparation of a high porosity compressed tablet using sublimating/ volatilizing agent (Camphor)

Table 1: Composition of eight different formulations of Domperidone ODTs

Ingredients	Formulation Code (mg / Tablet)							
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
Domperidone	10	10	10	10	10	10	10	10
Camphor	15	15	15	15	15	15	15	15
Ispaghula Husk	-	-	-	-	35	40	45	50
Povidon (Kollidon 30)	35	40	45	50	-	-	-	-
Guar Gum	10	10	10	10	10	10	10	10
Avicel PH 101	50	50	50	50	50	50	50	50
Kollidon CL	50	45	40	35	50	45	40	35
Aspertame	20	20	20	20	20	20	20	20
Mannitol	100	100	100	100	100	100	100	100
Cab-o-Sil	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2
Mg-stearate	2	2	2	2	2	2	2	2
Orange Flavor	3	3	3	3	3	3	3	3
Total	300	300	300	300	300	300	300	300

Evaluation of Granules

Angle of repose

Angle of repose (θ) was determined using fixed funnel method. 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 granular cone was measured and angle of repose was calculated using the following equation [25].

$\theta = \tan^{-1} (h/r)$ Where, h and r are the height and radius of the cone.

Carr's compressibility index

The simplex way of measurement of the free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index of the granules was determined by Carr's compressibility index (I) which is calculated by using the following formula [25].

CI (%) = (TD - PD) X 100 / TD Where, TD = Tapped Density, PD = Poured Density, CI = Carr's compressibility index.

Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula [25].

Hausner Ratio = TD/PD Where, TD = Tapped Density, PD = Poured density.

Tapped Density

Tapped density is the ratio between mass of granules and volume of the granules after tapping. It is expressed by gm/cc [25].

Tapped Density = Weight of granules/ Tapped volume

Evaluation of tablets

Tablet hardness

The strength of tablet is expressed as tensile strength (kp). The tablet crushing load, which is the force required to break a tablet by compression. The hardness of the tablets was determined by diametral compression using Pharmatest, hardness tester (Model no 1101, Germany) [26].

Tablet thickness

Tablet thickness can be measured using a simple procedure. 5 tablets were randomly taken from each formulation and their thickness was measured using Varnier calipers. The thickness was measured by placing tablet between two arms of the Varnier calipers [26].

Tablet Friability

The friability of the tablets was measured in a Pharma Test (Germany). Tablets of a known weight (W_0) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below [25].

$$\% \text{ of friability} = W_0 - W \times 100 / W_0$$

Determination was made in duplicate.

Weight variation test

The weights were determined by using Denver Instrument (Model-M-310). Weight control is based on a sample of 20 tablets. Determination was made in duplicate [25].

In vitro Wetting time (WT) study

The wetting time of the ODT tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a Petri dish with a 10 cm diameter. 10mL of Phosphate buffer solution simulating saliva pH 6.4 is added to Petri dish. A tablet is carefully placed on the surface of the tissue paper (Figure 3). The time required for water to reach upper surface of the tablet is noted as a wetting time. Determination was made in duplicate [27].

Table 2: Flow characteristics of powders for formulations (F-1 to F-8)

Formulation Code	Average Angle of repose(θ)	Average Carr's Index (%)	Average Hausner Ratio
F-1	29.25	16.56	1.20
F-2	27.47	18.79	1.23
F-3	27.92	20.12	1.25
F-4	28.8	21.47	1.27
F-5	30.11	21.34	1.27
F-6	27.21	20.23	1.24
F-7	28.35	21.02	1.27
F-8	29.83	21.98	1.28

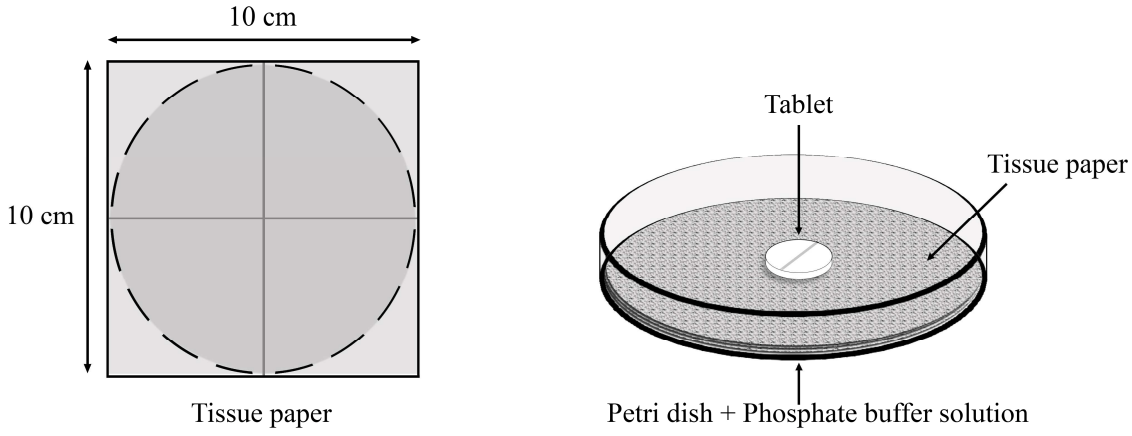

Fig. 3: Schematic illustration of the determination of tablet wetting time

In vitro Disintegration Time (DT) Study

The study was conducted by using PHARMA TEST disintegration test apparatus (Model No: D-63512, Hainburg). The apparatus consists of six plastic tubes which are open at one end and the other end is fitted with a rust proof No. 10 mesh.

The tubes are suspended in the Phosphate buffer solution (simulated saliva pH 6.4) at a temperature of 37± 2° C. The plastic tubes were allowed to move up and down at a constant rate 29-32 times per minute through a distance of 75 mm. The test was carried out on three tablets of each formulation code and the disintegration times (second) were noted [28].

In vitro dissolution study

Dissolution studies were conducted according to USP method (USP XXII) using apparatus II paddle method with 900mL 0.1N HCl solution at 37°C±0.5°C and 50 rpm. At 2, 5, 7 and 10 minutes interval samples of 10mL were withdrawn from the dissolution medium and were replaced with fresh medium to maintain the volume constant. The samples were filtered through a 0.45µ membrane filter. Then samples were diluted to a suitable concentration with 0.1 N HCl solutions [29]. The absorbance of the solutions was measured at 284 nm for drug Domperidone by using a HACH UV/Visible spectrophotometer (Germany). The cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

Table 3: Physical Characterization of oral dispersible tablets (F-1 to F-8)

Formulation code	Hardness (Kg/cm²)	Thickness (mm)	Diameter (mm)	Friability (%)	Average weight of each formulation (mg/tab)	Weight variation (%)	Wetting Time (Second)	DT (Second)
F-1	4.0	2.52	10.70	0.44	299	0.01	29	24
F-2	4.1	2.53	10.74	0.49	301	0.02	37	28
F-3	3.9	2.52	10.77	0.54	301	0.01	44	34
F-4	4.2	2.50	10.77	0.45	300	0.01	47	38
F-5	4.2	2.53	10.76	0.48	294	0.02	33	27
F-6	4.1	2.52	10.77	0.43	301	0.01	31	25
F-7	4.2	2.52	10.75	0.47	301	0.02	42	32
F-8	4.2	2.53	10.76	0.56	299	0.01	48	39

Kinetic modeling of drug release

After completing *in vitro* dissolution of all the batches for eight hours, the data were treated with zero-order equation [30] and Higuchi equations [31] respectively.

$M_t = M_0 + k_0 t$ … … … … … … … (1)

$Mt = M_0 - k_H t^{1/2}$ …. … … … … …. (2)

In these equations, M_t is the cumulative amount of drug released at any specified time (t) and M_0 is the dose of the drug incorporated in the delivery system. k_0 and k_H are rate constants for zero-order and Higuchi model respectively. These models failed to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore the dissolution data were also fitted to Korsmeyer kinetic equation [32] to ascertain the mechanism of drug release:

$\log (M_t/M_\infty) = \log k + n \log t$ … … … … … (3)

Where M_∞ is the amount of drug release after infinite time, k is the release rate constant which considers structural and geometric characteristics of the tablet, and n is the diffusion exponent or release exponent, indicative of the mechanism of drug release. For a tablet having cylindrical shape, when n is below 0.45, the Fickian diffusion phenomenon dominates, and n between 0.45 and 0.89 is an anomalous transport (non-Fickian diffusion), often termed as first-order release. After the n value reaches 0.89 and above, the release can be characterized by case II and super case II transport, which means the drug release rate does not change over time and the release is characterized by the zero-order. In this case, the drug release is dominated by the erosion and swelling of the polymer [33, 34].

Mean dissolution time (MDT) value is used to characterize the drug release rate from the dosage form and the retarding efficiency of the polymer. A higher value of MDT indicates a higher drug retaining ability of the polymer and vice-versa. The MDT value was also found to be a function of polymer loading, polymer nature and physico-chemical properties of the drug molecule.

Mean dissolution time (MDT) was calculated from dissolution data according to Mockel and Lippold [30] using the following equation:

$MDT = (n/n+1).\ K^{-1/n}$ … … … … … (4)

Table 4: Kinetic parameters of Domperidone release from the proposed formulations (F-1 to F-8)

Formulation Code	% of drug release after 10 min.	Zero Order		Higuchi		Korsmeyer		Mean Dissolution Time (MDT) (min)
		Ko	R^2	K_H	R^2	n	R^2	
F-1	84.22	8.6064	0.8718	29.029	0.9647	0.6317	0.9256	3.580
F-2	80.28	8.2491	0.8823	27.616	0.9618	0.6805	0.9253	4.107
F-3	81.06	8.2479	0.9119	27.786	0.9640	0.7453	0.9472	4.388
F-4	74.81	8.0026	0.9037	26.204	0.9424	0.8533	0.9289	5.084
F-5	83.44	8.4067	0.8548	28.672	0.9671	0.5662	0.9233	3.293
F-6	88.19	8.8613	0.8020	30.859	0.9460	0.5038	0.8748	2.479
F-7	84.97	8.294	0.921	27.957	0.9624	0.7930	0.9311	4.263
F-8	81.70	8.012	0.929	27.451	0.9388	0.8941	0.9285	5.277

RESULTS AND DISCUSSION

In the present study, oral dispersible tablets of Domperidone were prepared by using Kollidon CL (Crospovidone) as superdisintegrants. These directly compressed eight formulations were prepared by sublimation technique. The data obtained from pre-compressional parameters such as angle of repose, Carr's index and Hausner ratio were found to be within acceptable pharmacopoeia range (Table 2). Though some formulations showed good flow properties, glidant was added generally to improve flow properties of all formulations.

The compressed tablets were evaluated for physical properties like hardness, thickness, diameter, friability, weight variation , wetting

time and disintegration time and the results are tabulated in Table 3. The hardness was in the range of 3.9 to 4.2 Kg/cm². The average % friability was found 0.48%, which was well within the acceptable range of 1% and indicates the tablet surfaces are strong enough to withstand mechanical shock or attrition during storage and transportation until they are consumed. The average diameter and thickness were found as 10.75 mm and 2.52 mm for all formulations. Uniformity of weight was found to be in the range of 0.01% to 0.02% of weight variation.

The wetting time for all the formulated tables was in the range of 29 to 48 sec (Table 3). Disintegration time was calculated taking single tablets from each formulation. F-1 was found to be disintegrated quickly (24 seconds). As a significant amount of disintegrant (Kollidon CL, 50 mg) was used in that formulation. In case of F-2, F-3 and F-4, the mouth dissolving formulations showed slightly greater disintegration times due to the rise of binder (Kollidon 30) and lowering of disintegrant concentrations rather than the F-1. Similarly, F-6 was found to be disintegrated quickly (25 seconds) as a significant amount of disintegrant (Kollidon CL, 45 mg) and binder (Ispaghula husk, 40mg) was used in that formulation. As 5 tons pressure was applied to prepare Orally Disintegrating Tablets, the applied pressure showed to have an impact on the disintegration time of the tablets. The disintegration time was well within the acceptable range of less than a minute as per the compendia indicated. This rapid disintegration of tablets in oral cavity is contributed to pores, which are created in the tablet upon sublimation from the compressed tablets. This enhanced porosity allowed the saliva to penetrate into tablet and resulted into quick disintegration of tablet.

The *In vitro* release studies for the all eight formulations were shown in Table 4.

Effects of Kollidon 30 and Kollidon CL (Crospovidone) on the release kinetics of Domperidone Orally Disintegrating Tablets (F-1 to F-4)

From the Table 4 and Figure 4, release profiles of Domperidone from Kollidon 30 and Kollidon CL based ODTs of four different formulations were obtained. F-1 gave maximum release (84.22%) of Domperidone at 10 minutes due to presence of 50 mg of Kollidon CL, a superdisintegrant. it was observed that drug release rate has been decreased with increase in the amount of Kollidon 30 as the decrease in the amount of Kollidon CL, a binder. So from the experiment, it has been observed that the superdisintegrant attributes a direct impact over the drug release from the matrix of Domperidone mouth dissolving formulations.

Effects of Ispaghula husk and Kollidon CL (Crospovidone) on the release kinetics of Domperidone Orally Disintegrating Tablets (F-5 to F-8)

From the Table 4 and Figure 5, release profiles of Domperidone from Ispaghula husk and Kollidon CL based ODTs of four different formulations were obtained. F-6 gave 88.19% release of Domperidone at 10 minutes. So, it was observed that drug release rate has been decreased with increase in the amount of Ispaghula husk; however the amount of disintegrant is decreased.

So from the experiment, it has been observed that both the binder Kollidon 30 and Ispaghula husk attributes a direct impact over the drug release from the matrix of Domperidone mouth dissolving formulations and the disintegrant concentration is dominated by the amount of binder used.

The MDT value was also found to be a function of polymer content and polymer nature. MDT values for all the eight formulas are listed in Table 4. From the table, it was observed that, F-1 to F-8 best fits with Higuchi kinetic model. The value of release exponent (***n***) obtained from F-1 to F-7 were in the range of 0.5038~0.8533 which indicates that the release pattern of Domperidone followed anomalous/ non-Fickian transport mechanism, which appears to indicate a coupling of the diffusion and erosion mechanism.

Whereas the values of release exponent (n) obtained from F-8 were 0.8941 which indicates that the drug was released from F-8 followed the super case II transport pattern.

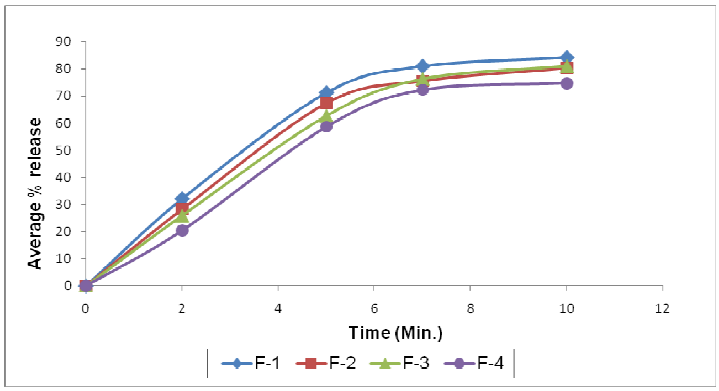

Fig. 4: Zero order release profiles of Domperidone Orally Disintegrating Tablets (F-1 to F-4)

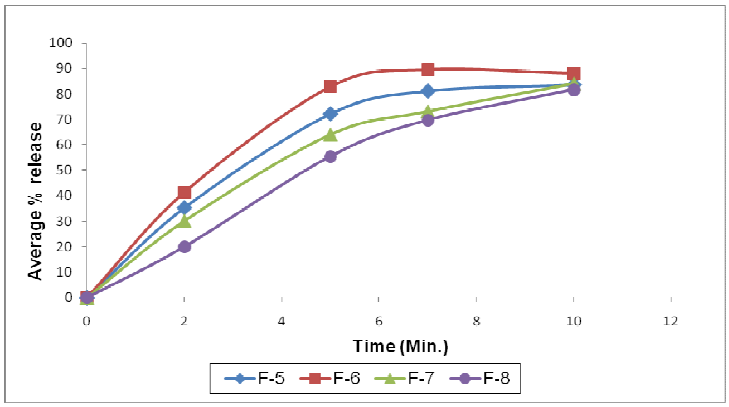

Fig. 5: Zero order release profiles of Domperidone Orally Disintegrating Tablets (F-5 to F-8)

CONCLUSION

In recent years, considerable attention has been focused on the development of novel drug delivery systems (NDDS) [35]. Among various methods being studied and developed fast disintegrating dosage forms have been successfully commercialized, and these dosage forms very well accepted at doctors as well as patient level [36].

The present study was conducted to evaluate the disintegration time (DT) and the percent release of drug from the Domperidone ODTs containing different percentage of disintegrants and rate retarding polymers. The experiment indicates that, it is possible to design Domperidone ODT by sublimation method with a proper hardness and acceptable friability ranges that are able to disintegrate within the acceptable time range as defined by the FDA.

The study reveals that oven-drying technique showed better disintegration and drug release and would be an effective alternative approach compared with the use of more expensive adjuvant in the formulation of ODTs. Formulation F-1 containing Kollidon 30 against Kollidon CL showed the DT of 24 seconds with an adequate drug release of more than 84%. On the other hand, formulation F-6 having Ispaghula husk against Kollidon CL showed 25 seconds of DT with an immediate drug release of more than 88%.

It is thus concluded that, the disintegration time of Domperidone ODTs depend upon the types and amount of disintegrants incorporated against rate retarding polymers or binders. The rate retarding polymers were basically incorporated as binders for the powdered materials but it was observed that, the disintegrating agents were successively overcome their drug retarding capacity and gave the drug release of more than 88% at the site of absorption within ten minutes only. Undoubtedly the availability of various technologies and the manifold advantages of ODTs will surely enhance the patient compliance, low dosing, rapid onset of action, increased bioavailability, low side effect, good stability and its popularity in near future.

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