



FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF DIMENHYDRINATE BY USING CO-PROCESSED SUPERDISINTEGRANTS

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ABSTRACT

The main objective of this study was to formulate orodispersible tablets of Dimenhydrinate for quick relief of emesis. Orodispersible tablets were prepared by direct compression method using co-processed super-disintegrants. Co-processed super-disintegrants are the mixture of croscopovidone and guar gum in different ratios. The powder mixtures and tablets were subjected to various pre-compression and post-compression evaluations. IR spectroscopy showed no interaction between drug and other excipients. Angle of repose and Carr's index was found in the range of 23.89°-28.27° and 23.29-15.48 respectively. These results indicated that powder mixtures showed good to acceptable flow properties. All formulations containing co-processed super-disintegrant showed short disintegration time (38.23-17.67 s) and maximum water absorption ratio 73.39%-91.35% compared to control formulation (3.54 min wetting time). Among all formulation F7 containing croscopovidone: guar gum in 1:3 ratio showed highest percentage of drug release (98.89%) in 30 min, which is due to high degree of swelling caused by guar gum along with rapid hydration of tablets by croscopovidone. Formulation F7 was subjected for 3 months of stability studies; results revealed that the tablet formulation was stable throughout the study period. In conclusion the obtained results suggested that orodispersible tablets of Dimenhydrinate with rapid disintegration and fast drug release can be successfully formulated by employing co-processed super-disintegrants.

Keywords: Co-processed super-disintegrants, Dimenhydrinate, Direct compression, Disintegrating time.

INTRODUCTION

Even though there are many routes of drug administration, oral route of drug administration is most popular route. Oral route of drug administration is accepted by wide range of population due to its safety, most convenient, pain less and low cost ^[1].

Among all solid oral dosage forms, tablet is most popular because of self-medication, compactness and ease of manufacturing. The main problem of the tablet in relation with patients is dysphagia (difficulty in swallowing). According to a survey dysphagia is common in about 35% of the general population and additional 30-40% of elderly institutionalized patients who express difficulty in swallowing tablets, resulting in noncompliance and ineffective therapy. Geriatric, paediatric and travelling patients who may not have ready access to water are most in need of easy swallowing of tablets ^[1, 2].



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To overcome the above problems, scientists have developed an innovative drug delivery system that can dissolve or suspend tablets in the mouth for easy swallowing. Such tablets are known as orodispersible tablet (FDTs) [3]. Orodispersible tablet is approved by recognized regulatory agencies like United States Food and Drug Administration (FDA) and European Pharmacopeia, where FDA defines orodispersible tablets as “a solid dosage form containing medical substances which disintegrate rapidly when placed upon the tongue” [2]. Disintegration time for such orodispersible tablet varies from few seconds to about a minute which results easy swallowing of tablets and also plays important role in drug absorption through buccal cavity, thus increases bioavailability by bypassing hepatic metabolism of drugs [4].

Vomiting problem is seen in all group of population and occurs due to stimulation of the chemoreceptor trigger zone (CTZ) (vomiting centre) situated in the medulla oblongata. The CTZ express a variety of receptors, e.g., histamine H1, dopamine D2, serotonin 5-HT3, cholinergic M and opioid μ through which the emetic signals are relayed and which could be targets of antiemetic drug action [5].

Dimenhydrinate is chemically, 8-chloro-1, 3-dimethyl 1-2, 6-dioxo-2, 3, 6, 7-tetrahydro-1h-purin-7ide; [2(diphenylmethoxy) ethyl] dimethyl azanium. It is a salt of diphenhydramine and chlorotheophyllinate. Dimenhydramine is an antihistaminic drug that is antagonistic at the H1 receptor in order to prevent or suppress nausea and vomiting. Chlorotheophyllinate is added in order to counteract drowsiness caused by diphenhydramine. Dimenhydrinate is freely soluble in alcohol, chloroform and sparingly soluble in water (about 3mg/ml). It is having 2-3 hrs of self-life with fast onset of action after its oral administration [6, 7].

Co-processing method is new and novel concept, where more than one excipient interacts each other at the sub particle level and hence masks the undesirable properties of an individual excipient. Co-processed excipients so formed are superior in many properties such as improved flow properties, compressibility, and better dissolution profile and reduced lubricant sensitivity compared with individual excipients or physical mixtures of excipients [8]. Commercially several co-processed superdisintegrants are available, some of them includes Ludipress (lactose monohydrate, polyvinylpyrrolidone and crospovidone), Ran Explo-C (microcrystalline cellulose, silica, crospovidone), Starlac (lactose and maize starch), Ludiflash (mannitol, polyvinyl acetate and crospovidone), F-melt, Pharma burst, Pan Excea MH300G, Pearlitol 200 SD and so on. In this present study, an approach has made for preparation and evaluation of Dimenhydrinate FDTs using co-processed super-disintegrants containing crospovidone and guar gum. The reasons of selecting crospovidone are high capillary activity, pronounced hydration and little tendency to form gels. Guar gum was selected due to its swelling and wicking capacity [8, 9].

The main aim formulating orodispersible tablet of Dimenhydrinate using co-processed super-disintegrants are to increase the water uptake with shortest wetting time and disintegration time of the prepared tablets which in turn improve dissolution rate and hence its bioavailability.



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MATERIAL AND METHODS

Drugs and chemicals:

Dimenhydrinate was obtained as gift sample from S.S Pharma, Mumbai (India), Crospovidone, Guar gum, were procured from S.D finechem limited, Mumbai (India), Magnesium stearate, Aspartame and Mannitol were analytical grade.

Fourier transform infrared spectroscopy (FTIR):

If the excipients are new and are not used in formulations containing the active substance, the compatibility studies are of paramount importance. IR spectra of the pure drug and the physical mixture of drug and excipients were conducted using a Thermo Nicolet FTIR and the spectrum was recorded in the region of 4000 to 400 cm^{-1} . All spectra were collected as an average of three scans at a resolution of 2 cm^{-1} .

Preparation of co-processed super-disintegrants:

The co-processed super-disintegrants were prepared by solvent evaporation method using chloroform as volatile solvents. Crospovidone and guar gum were mixed together with 10-15 ml of chloroform in different ratio as shown in Table 1. The solutions were stirred thoroughly till almost all chloroform evaporated. The wet coherent mass was then granulated through sieve # 60.

The wet granules were dried in a hot air oven at 60°C for 30 min. The dried granules were again passed through sieve # 60 in order to break lumps and then stored in airtight container for further use.

Table 1: Composition of co-processed super-disintegrants of crospovidone and guar gum

Mixture code	C1	C2	C3	C4	C5
Crospovidone	1	2	3	1	1
Guar gum	1	1	1	2	3

Preparation of Dimenhydrinate orodispersible tablets

Orodispersible tablets of Dimenhydrinate were prepared by direct compression. Compositions of Dimenhydrinate FDTs were dissipated in Table 2. Each formulation contains 50mg of pure drug. In all formulations mannitol was used as diluent, aspartame as sweetening agent, magnesium stearate as well as talc as lubricants and menthol as flavouring agent. The calculated quantity of drug and excipients were weighed accurately and passed through sieve # 60 separately. Sieved powder materials were transferred to mortar in geometrical dilution order and mixed well for about 10 min and at the end of mixing lubricants were added and further mixed for 5 min. Finally, physical mixtures were compressed into tablets using single punch tablet machine (Lab Press, India) using 8mm flat surface punches under 2-4 kg/cm^3 compression force. Formulation F0 does not contain any super disintegrating agent, whereas F1 and F2 possess 5mg of guar gum and crospovidone respectively. In F3, F4, F5, F6 and F7 formulations, 5mg of C1, C2, C3, C4 and C5 co-processed superdisintegrants were present respectively.



Table 2: Composition of Dimenhydrinate FDTs prepared by direct compression method

Ingredients (mg)	Formulation code							
	F0	F1	F2	F3	F4	F5	F6	F7
Dimenhydrinate	50	50	50	50	50	50	50	50
Crospovidone	-	-	5	-	-	-	-	-
Guar gum	-	5	-	-	-	-	-	-
Co-processed superdisintegrant	-	-	-	5	5	5	5	5
Micro crystalline cellulose (MCC)	10	10	10	10	10	10	10	10
Aspartame	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Menthol	1	1	1	1	1	1	1	1
Magnesium stearate	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1
Mannitol up to	150	150	150	150	150	150	150	150

All quantities in milligram (mg).

Pre-compression evaluation parameters:

Before compression, powder mixtures were evaluated for pre-compression parameters such as angle of repose (Θ), bulk density (D_v), true density (D_t), compressibility index (CI) and Hausner ratio (H). From above parameters flow properties and compressibility properties of powder mixtures were determined. Angle of repose was determined by funnel method. Bulk density and Tapped density was determined by bulk density apparatus^[10, 11].

Post compression parameters of prepared tablets:

After compression, prepared tablets were subjected for various tests such weight variation, thickness, hardness, friability, wetting time, water absorption ratio, drug content, disintegrating time^[12, 13, 14, 15].

Drug content estimation:

Randomly 20 tablets were taken, weighed and powdered. The powder equivalent to 100 mg drug was weighed accurately and dissolved in 100ml of phosphate buffer 6.8. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatmann No.41 filter paper. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 278nm. The concentration of the drug was computed from the standard curve of the Dimenhydrinate [15].

In-vitro drug release study:

In- vitro dissolution studies carried out using USP type II paddle type dissolution apparatus (Lab India). The dissolution medium used was pH 6.8 phosphate buffer (900ml) maintained $37 \pm 5^\circ\text{C}$ with a paddle rotation speed at 50 rpm. 10ml sample was withdrawn at predetermined time interval 1, 5,



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10, 15, 30 min and replaced with same volume of fresh dissolution medium. Absorbance of this solution was measured at 278 nm using UV-Visible spectrophotometer-1800 (Shimadzu, Japan). Drug concentration was calculated and expressed as cumulative percentage of the drug released^[1].

Drug release kinetics:

The cumulative amount of drug release from the formulated tablets were fitted to zero order kinetics, first order kinetics, Higuchi's model and Korsmeyer-Peppas model to characterize *in-vitro* drug release mechanism^[1].

Stability testing:

Stability studies of the formulated Dimenhydrinate orodispersible tablets were carried out at 25°C/60 %RH and 45°C/75 %RH in stability chamber (LAB TOP, Mumbai) for period of 3 month (mo). Tablets were withdrawn periodically at 1, 2 and 3 mo respectively and evaluated for % weight increase, friability, drug content, and *in-vitro* dissolution studies^[16].

RESULT AND DISCUSSION

A simple technique of direct compression was used in present study for the preparation of Dimenhydrinate orodispersible tablets. Direct compression was choice for preparation of Dimenhydrinate orodispersible tablets because this method required preliminary granulation or agglomeration process for tableting of a blend of ingredients. Orodispersible tablets of Dimenhydrinate were prepared by using co-processed super-disintegrants i.e. crospovidone: guar gum in 1:1, 2:1, 3:1, 1:2 and 1:3 ratios. MCC was used as direct compressible material due to its broad spectrum properties like dry binding, broad compatibility with AIPs, inertness, ease of handling and self-disintegrating with low lubricant requirement properties. Mannitol was used as filler as it imparts multifunctional benefits such as easy availability, good aqueous solubility and wetting properties facilitating tablet breakdown as well as negative heats of solution giving cooling effect in the mouth. Slight bitter taste of the tablet has been masked by using aspartame; sugar-free sweetener.

Pre-compression evaluation:

Fourier transform infrared spectroscopy (FTIR):

IR spectra of Dimenhydrinate and its excipients used in preparation of Dimenhydrinate orodispersible tablets were determined by FTIR spectroscopy to examine the compatibility and are dissipated in Fig. 1-2. The characteristics peak of Dimenhydrinate at 3387.43 cm^{-1} corresponding to its amino group was detected in all physical mixture. The pure drug also showed sharp stretching peaks at 1687.77 cm^{-1} for (C=O), at 1520.44 cm^{-1} for (C=C) stretching of the aromatic rings, at 751.30 cm^{-1} for (C-Cl) stretching of the carbonyl chloride. The results of FTIR spectroscopy showed that IR spectrum of Dimenhydrinate and its physical mixture with excipients showed the same characteristics bands of the drug in the same regions and at same ranges, thus indicating no significant interaction between the drug and excipients used.



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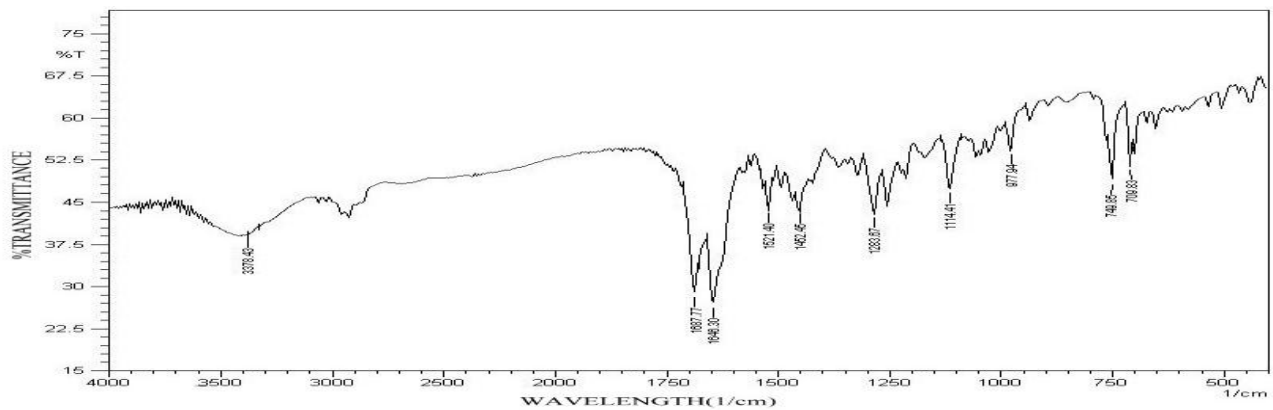


Figure 1. FT-IR spectrum of drug

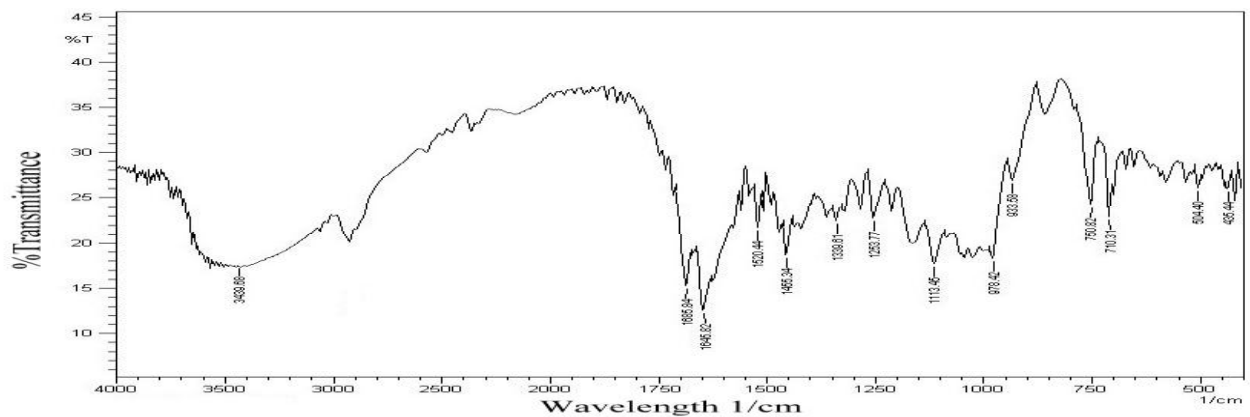


Figure 2. FT-IR Spectrum of drug + physical mixture of excipients

Micro meretics study of powder mixtures:

In this present study, micro meretics studies were performed for all formulations and results obtained are dissipated in Table 3. Angle of repose (Θ) deals with the internal friction or cohesion of the particles. If the value of angle of repose is high, powder is cohesive and lower value indicates non-cohesive property of powder mixture. Formulations containing co-processed super-disintegrants showed lower values (23.89° to 28.27°) of angle of repose compared to control formulation (38.42°), hence all formulations showed good to acceptable flow properties (Escubed Ltd). Carr's index (23.29 to 15.48) showed all the formulations exhibits acceptable too good flowability. Haunser showed that powders with low inter-particle friction had ratios below 1.25. Hence all the formulation exhibits low inter-particle friction; as the value of Haunser ratio (1.183-1.23) was lower than state limit i.e. 1.25.



Table 3: Pre-compression evaluation results

Formulation code	Angle of repose(Θ)	Bulk Density(g/ml)	Tapped Density(g/ml)	Carr's Index	Hauser ratio
F0	38.42 \pm 0.032	0.367 \pm 0.032	0.439 \pm 0.042	23.29 \pm 0.35	1.185
F1	27.56 \pm 0.022	0.337 \pm 0.087	0.434 \pm 0.018	15.61 \pm 0.14	1.203
F2	28.72 \pm 0.014	0.397 \pm 0.032	0.440 \pm 0.0091	15.48 \pm 0.21	1.183
F3	25.94 \pm 0.19	0.367 \pm 0.061	0.470 \pm 0.021	17.60 \pm 0.09	1.210
F4	24.18 \pm 0.087	0.483 \pm 0.043	0.441 \pm 0.032	19.11 \pm 0.14	1.230
F5	23.89 \pm 0.26	0.338 \pm 0.073	0.541 \pm 0.230	18.38 \pm 0.04	1.220
F6	26.24 \pm 0.08	0.341 \pm 0.007	0.415 \pm 0.051	18.02 \pm 0.08	1.219
F7	26.45 \pm 0.041	0.420 \pm 0.028	0.416 \pm 0.081	16.83 \pm 0.05	1.202

Post-compression evaluation:

As the powder mixtures showed good flow properties, tablet produced were of uniform weight (148.32mg-152.76mg) due to uniform die filling of punching machine. Hardness of the tablets was found to vary from 2.67 to 3.52 kg/cm² compared to 2.15kg/cm² of control tablets. Thickness of tables for all formulation was approximately 3.34 mm. Hardness and thickness of tablets was suitable for packaging and handling. The % friability was less than 1% for all formulation (IP, BP, and USP) indicates that tablets formulations are of good mechanical strength to withstand abrasion in handling. Drug content was found in the range of 97.26%-101.54% which was under pharmacopoeial limits. Water absorption ratio and wetting time were found in the range of 73.39-91.35% and 38.23-17.67s respectively compared to 3.54 min (wetting time) of control formulation. Among all, formulation containing crospovidone: guar gum (1:3) showed the highest water absorption percentage (91.35%) and lowest wetting time (17.67s). These results were correlated with disintegration time results. Formulation which showed higher wetting time required more time to disintegrant and vice versa. The decrease in disintegrating time of formulation containing co-processed super-disintegrant was found compared to control formulation. This could be due to rapid water absorption and swelling capacity of super-disintegrant, which results in rapid breakdown of tablets (Naikwade JT et al). F7 showed lowest disintegration time (17.67s, according to European Pharmacopoeia time required is less than 3 minutes) which may be due to higher capillary action of crospovidone along with swelling ability of guar gum, which together causes fast rupturing of tablets. The results of post-compression evaluation were dissipated in Table 4.

Table 4: Post-compression evaluation results

Formulation code	F0	F1	F2	F3	F4	F5	F6	F7
Weight variation	149.55 \pm 0.25	151.12 \pm 0.33	148.32 \pm 0.37	152.76 \pm 0.28	150.74 \pm 0.63	148.54 \pm 0.42	151.78 \pm 0.32	150.92 \pm 0.53
Thickness (mm)	3.42 \pm 0.032	3.34 \pm 0.012	3.36 \pm 0.05	3.32 \pm 0.047	3.44 \pm 0.091	3.23 \pm 0.071	3.34 \pm 0.088	3.24 \pm 0.091
Hardness kg/cm ²	2.15 \pm 0.145	2.48 \pm 0.113	2.57 \pm 0.18	3.31 \pm 0.152	2.93 \pm 0.132	3.12 \pm 0.196	3.39 \pm 0.158	3.52 \pm 0.16
% Friability	0.73 \pm 0.019	0.69 \pm 0.023	0.71 \pm 0.05	0.61 \pm 0.037	0.65 \pm 0.042	0.62 \pm 0.033	0.68 \pm 0.054	0.77 \pm 0.04



Water absorption ratio	53.15 ± 0.182	62.98 ± 0.513	67.72 ± 0.37	73.39 ± 0.425	75.12 ± 0.433	82.20 ± 0.230	85.99 ± 0.146	91.35 ± 0.62
Disintegration time (S)	180.54 ± 0.550	56.32 ± 0.710	44.63 ± 0.64	39.23 ± 0.630	28.88 ± 0.194	27.00 ± 0.541	20.78 ± 0.682	17.37 ± 0.79
% Drug content	98.51 ± 0.031	97.88 ± 0.022	102.10 ± 0.05	96.99 ± 0.048	101.47 ± 0.037	97.65 ± 0.016	100.10 ± 0.028	102.46 ± 0.07
% Weight increased (after 1 month)	0.23 ± 0.730	0.31 ± 0.520	0.37 ± 0.59	0.401 ± 0.514	0.42 ± 0.640	0.46 ± 0.334	0.49 ± 0.320	0.51 ± 0.52

***In-vitro* dissolution study:**

The dissolution study of Dimenhydrinate was carried out in phosphate buffer pH 6.8 for the period of 30 min. F0 represents control formulation to which dissolution profile of other formulations were compared. The results obtained from the dissolution study are dissipated in Figure 4. F0 showed minimum cumulative % drug release (65.21%) over a period 30 min because of absence of super-disintegrants. F1 and F2 contains crospovidone and guar gum as super-disintegrants in same concentration respectively. The amount of drug release from these preparations was comparatively higher than control formulation. F3, F4, F5, F6 and F7 prepared by using co-processed super-disintegrant was found to release 96.16, 96.87, 97.32, 98.31, 98.89% respectively, at the end of 30 min. In all formulations (except control, F1 and F2) the cumulative % drug release was closer to 100% within 30 min which might be due to rapid breakdown of particles of co-processed super-disintegrants and porous structure of the tablets. F7 showed maximum percentage of drug release (98.89%) which could be due to presence of higher concentration of guar gum along with optimum level of crospovidone compared to other formulations. Elbary AA et al stated that crospovidone increases water absorption ratio of tablet formulation by its hydration effect and guar gum swells in such extent that tablets break rapidly into particles. This is the main reason for higher % of drug release from the tablet formulation F7. The formulation F7 was selected for *in-vitro* drug release kinetic studies and stability studies on the basis of its high cumulative % drug release.

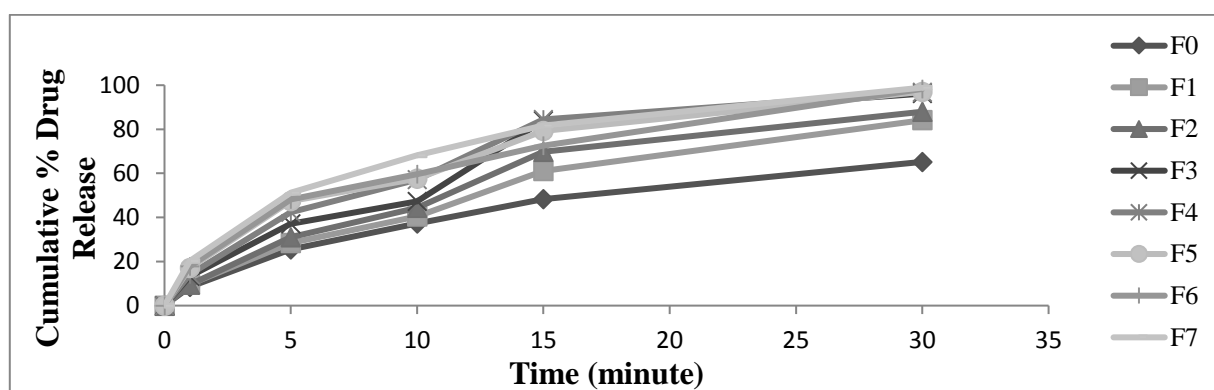


Figure 4. Comparative dissolution rate profile of Dimenhydrinate orodispersible tablets (Batch F0 to F7)



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Stability study:

A stability study was conducted at 25°C/60% RH and 40°C/75% RH for the period of 3 months. F7 was selected for stability studies and results showed no significance changes in colour, appearance, % friability and wetting time throughout the study. There was no significant change ($P=0.0124$, i.e. ≤ 0.05) in the dissolution rate profile of Dimenhydrinate from its FDTs stored at 25°C/60% RH and 45°C/75% RH. Results also showed that only 1.32% drug degradation was observed at the end of 3 months. The weight of tablets was increased up to 1% after 3 months, which could be due to hydration effect of co-processed super-disintegrants. Hence, prepared tablet formulation was stable and further stability can be maintained by specialized packaging and storage condition. Results for the stability study are shown in Table 6. Kinetic release studies of the stability data obtained from formulation F7 indicates that the drug degradation follows first-order kinetics. It was found that the value of 'R²' for first-order kinetics is 0.9937, which is near to 1 when compared to Higuchi square root (0.9707) and Zero order kinetic (0.8239) model. Table 7 shows data for kinetic release studies at 25°C and 60% RH. Korsmeyer-Peppas model showed "n" value of 0.9998 for formulae F7, which indicates that the drug release followed super case II transport.

Table 6: Results of stability studies under various storage conditions

Stability period	Stability conditions							
	25°C/60% RH				45°C/75% RH			
	% Weight increased	% Friability	% Drug content	Dissolution Profile	% Weight increased	% Friability	% Drug content	Dissolution profile
Initial	0	0.62	102.46	98.89	0	0.62	102.46	98.89
End of 1 st month	0.23	0.65	101.98	98.22	0.26	0.66	101.64	98.19
End of 2 nd month	0.67	0.71	101.87	98.04	0.72	0.74	101.39	97.54
End of 3 rd month	0.96	0.77	101.54	97.56	1.02	0.83	101.12	96.71

Table 7: *In-vitro* kinetic release studies of formulation F7

<i>In-vitro</i> release kinetic models					
Formulae	Zero order	First order	Higuchi	Korsmeyer-Peppas	
F7	R ²	R ²	R ²	R ²	N
	0.8239	0.9937	0.9734	0.6707	0.9998

CONCLUSION

Thus, FDTs of Dimenhydrinate could be considered safe and useful oral delivery system to increase the drug bioavailability and to improve patient compliance. From this study, it can be concluded that co-processed super-disintegrant of crospovidone and guar gum could be applied effectively in preparation of FDTs with better water absorption, disintegration and drug released properties. The



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prepared FDTs disintegrate within a minute; thereby enhance the absorption leading to increased bioavailability of Dimenhydrinate, hence gives quick relief from emesis.

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