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Selection of Superdisintegrants – A Study on Anti Emetic Mouth Dissolving Tablets Containing Promethazine Hydrochloride

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ABSTRACT

The present work describes the formulation development of mouth dissolving tablets of Promethazine HCl with an optimum dispersion time along with sufficient hardness. The formulation employed three different super disintegrants, namely crospovidone (CP), sodium starch glycolate (SSG) and crosscarmellose sodium (CCS), each in three different ratios. Microcrystalline cellulose and mannitol were used as binder and diluent respectively. FT-IR and DSC were used to study the drug-excipient compatibility. Preformulation studies were carried out so as to study the compression characteristics and the flow properties of the powder mix, which was within satisfactory limits. Formulations were made by direct compression method and evaluated for *in vitro* dispersion time (DT), hardness, friability, wetting time, and *in vitro* dissolution rate. The effect of DCP and lactose as a diluent was evaluated. All the formulations showed a DT below 4 min. with hardness of 2.9 $kg.cm^{-2}$ or above. Tablets containing CP at 10%W/W with a hardness of 3.25 $kg.cm^{-2}$ and DT of 17 S was chosen as the most satisfactory formulation which released the complete drug in 4 min. The other super disintegrants yield tablets of nearly lesser hardness (upto 2.9 $kg.cm^{-2}$) with higher DT (upto 216 S). DCP and lactose increased the DT without major effect hardness of tablets.

Keywords: Mouth dissolving tablets, super disintegrants, promethazine hydrochloride, *in vitro* dispersion time, wetting time.

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INTRODUCTION

Kinetosis or motion sickness is a common problem experienced by travellers.It is a condition in which a disagreement exists between visually perceived movement and the vestibular systems sense of movementee. The key to a successful drug delivery application is based on meeting the unmet need or benefit of use of the chosen system, that's why a technology selection process will be most successful when considering clinical, technical, medical, and business benefits. Bringing these four factors together, the selected drug delivery system will significantly enhance patient compliance and market acceptance. The most effective antidopaminergic agent currently approved for motion sickness is Promethazine hydrochloride (PM), a phenothiazine derivative with antihistamine, anticholinergic and sedative effects. It is useful for both active and prophylactic treatment of motion sickness.

Promethazine is a phenothiazine derivative with antihistamine (H1 receptor antagonist) and anticholinergic properties.[1,2] Clinically useful effects include anti-emetic, antihistamine and sedative effects. Its offensive taste and anesthetic effect coupled with its high water solubility (500 mg/ml) enable Promethazine HCl to be an excellent model for testing a mouth dissolving formulation.

Tablet dosage forms which disintegrate rapidly in the mouth and can be taken without water, have become extremely popular in recent years.[3] These products offer the advantages of a tablet with the ease of swallowing a liquid. These dosage forms are of particular advantage in certain patient groups such as children, elderly and psychiatric patients. Product life cycle management has led pharmaceutical companies to be very interested in using these dosage forms to extend brand name use after the initial dosage forms become available generically.[4-6]

Dysphagia is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. Solid dosage forms that can be disintegrated, dissolved or suspended by saliva in the mouth resulting in easy swallowing can provide significant benefits to the pediatric and geriatric population as well as other patients who prefer easily swallowable dosage forms. Mouth dissolving tablets disintegrate instantaneously when placed on tongue, releasing the drugs that dissolve or disperse in saliva.[7-9] Rapid dissolution of drug and absorption may produce rapid onset of action. Absorption of drug from buccal or oesophageal mucosa may increase the bioavailability by bypassing the hepatic first pass effect.[10-12]

Various approaches to formulate fast dissolving tablets have been studied, which contributed much to the pharmaceutical technology. Conventional technologies include lyophilization, moulding,

sublimation, spray drying, mass extrusion, cotton-candy process, direct compression etc. There are patented technologies in the market like Zydis technology, Orasolv technology, Durasolv technology, Wow tab technology, Flashdose technology, Flashtab technology, Shearform technology, Ceform technology, Nanocrystal technology and many more. In the present study, a direct compression method was adopted to achieve a harder fast dissolving tablet formulation of Promethazine HCl.

MATERIALS AND METHOD

Promethazine HCl was a kind gift sample from Medopharm, Malur. Crospovidone (CP), Croscarmellose sodium (CCS), Sodium starch glycolate (SSG) were purchased from Yarrow chem Pvt. Ltd, Mumbai. All the other excipients were purchased locally and were of analytical grade.

Analytical method development for estimation of promethazine HCl

50 mg of accurately weighed PM was dissolved in pH 6.8 and concentration of 2, 4, 6, 8, 10, 12 and 14µg/ml were produced by suitable dilutions. Solutions were scanned for their λmax in the range of 200-400 nm using Shimadzu 1800 UV-Visible spectrophotometer. Absorbance was measured at 249nm and a standard curve was plotted.

Drug polymer compatibility studies

Drug polymer compatibility studies were carried out using FTIR. Infra red spectrum of pure drug was derived in between 600 to 3800 cm-1. The study was carried out on individual pure drug and its physical mixture with the selected polymers under study.

Micromeritic Properties of precompression mix

Angle of repose

The angle of repose of powder was determined by the funnel method using the following equation

Angle of repose, $\theta = \text{Tan}^{-1}h/r$

Where, θ = angle of repose, h = height of the cone, r = radius of the cone base

Bulk density, Carr's index and porosity

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. It was determined by measuring the volume of powder before and after 300 tappings using Electolab tap density tester ETD-1020. The Carr's index of the powder mix was determined by using formula,

Carr's index (%) = [(TBD – LBD) × 100]/TBD

Where, LBD = weight of the powder/volume of the packing TBD = weight of the powder/tapped volume of the packing.

Porosity is the ratio of the total volume of void spaces to the bulk volume of the material. It is

often important because a fine capillary network of voids or pores has been shown to enhance the rate of liquid uptake by tablets, which in turn increases the rate of their disintegration.

Formulation of promethazine HCl mouth dissolving tablets

Various formulations of orally disintegrating tablets were developed for Promethazine hydrochloride by direct compression method using various superdisintegrants like crospovidone, sodium starch glycolate and croscarmellose sodium and Mannitol as a diluent. Microcrystalline cellulose was used as a binder. Dicalcium phosphate was an inorganic agent that does not react with water. Magnesium stearate was used as lubricant. Aspartame was added as a sweetening agent. Lactose was added as a diluent in selected formulations.

The entire formulations batch was prepared by direct compression technique. All ingredients were sieved through #60, and were weighed accurately. They were mixed thoroughly using geometric mixing. These powders were lubricated with magnesium stearate. The lubricated powders were compressed into tablets in 6 mm die cavity of rotary tablet punching machine.

Table 1: Formulation chart of promethazine HCl fast dissolving tablets

Ingredients	F11 (mg)	F12 (mg)	F13 (mg)	F14 (mg)	F21 (mg)	F22 (mg)	F23 (mg)	F31 (mg)	F32 (mg)	F33 (mg)
Promethazie HCl	25	25	25	25	25	25	25	25	25	25
Crospovidone	5.2 4%	7.8 6%	10.4 8%	13 10%	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	-	5.2 4%	7.8 6%	10.4 8%	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	-	3.9 3%	7.8 6%	11.7 9%
Mannitol	49.25	46.65	44.05	41.45	49.25	46.65	44.05	50.55	46.65	42.75
Microcrystalline Cellulose	45.5	45.5	45.5	45.5	45.5	45.5	45.5	45.5	45.5	45.5
Aspartame	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9
Magnesium stearate	1.15	1.15	1.15	1.15	1.15	1.15	1.15	1.15	1.15	1.15

Ingredients	F41 (mg)	F42 (mg)	F43 (mg)	F51 (mg)	F52 (mg)	F53 (mg)	F54 (mg)
Promethazie HCl	25	25	25	25	25	25	25
Crospovidone	13 10%	13 10%	13 10%	13 10%	13 10%	13 10%	13 10%
Dicalcium phosphate	6.5 5%	13 10%	19.5 15%	-	-	-	-
Lactose	-	-	-	13 10%	26 20%	39 30%	41.45
Mannitol	34.95	28.45	21.95	28.45	15.45	2.45	-
Microcrystalline cellulose	45.5	45.5	45.5	45.5	45.5	45.5	45.5
Aspartame	3.9	3.9	3.9	3.9	3.9	3.9	3.9
Magnesium stearate	1.15	1.15	1.15	1.15	1.15	1.15	1.15

*Quantities are mentioned for a single tablet.

Evaluation of physicochemical parameters of MDT

Evaluation parameters of tablets mentioned in the pharmacopoeia need to be assessed, but some, which require special concern or need to be modified, are discussed. Hardness, thickness, friability and weight variation of the tablets were measured by standard methods.

Uniformity of drug content

Five tablets were weighed and crushed and powder equivalent to 10 mg drug was dissolved in 10 ml of phosphate buffer pH 6.8. Suitable dilutions were made and absorbance was measured at 249nm using a UV visible spectrophotometer. Amount of drug present in one tablet was calculated by calibration curve method.

Rapidly disintegrating property

To evaluate the tablets for their rapid disintegration properties, following tests were carried out.

Wetting time[12]

Two circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten milliliters of water containing eosin, a water-soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Modified disintegration test (*In vitro* disintegration time)[13]

The standard procedure of performing disintegration test for these kind dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration time for MDT needs to be modified as disintegration is required to take place without much water, thus the test should mimic disintegration in salivary contents. For this purpose, a suitable beaker was filled with 10 ml of water. The tablet was carefully put in the center of the beaker and the time for the tablet to completely disintegrate into fine particles was noted.

***In vitro* drug release**

The *in vitro* release rate of Promethazine HCl from the mouth dissolving tablets was determined using USP dissolution testing apparatus II. The dissolution test was performed using 500 ml of phosphate buffer pH 6.8 at 37 ± 0.5°C and 50 rpm. Aliquots were withdrawn from the dissolution apparatus and the samples were replaced with fresh dissolution medium. After filtration, the amount of drug release was determined from the standard calibration curve of pure drug using UV Visible spectrophotometer.

Stability studies of the most satisfactory formulation

The most satisfactory formulation was sealed in aluminum packaging and kept in humidity chamber maintained at 30 ± 2°C / 65 ± 5% RH and 40 ± 2°C / 75 ± 5% RH for 3 months. At the end of studies, samples were analyzed for the drug content, *in vitro* dissolution, *in vitro* dispersion time and other physicochemical parameters.

RESULTS AND DISCUSSION

Three different super disintegrants namely, crospovidone, sodium starch glycolate and croscarmellose sodium were used in the formulation of fast dissolving tablets. A total of seventeen formulations were made by direct compression using microcrystalline cellulose as a binder.

Analytical method development for estimation of promethazine HCl

Promethzine hydrochloride showed maximum absorption at wavelength 249 nm in Ph 6.8 phosphate buffer. Calibration curve obeyed Beer's law in the concentration range of 2 to 14 µg /ml and when subjected to regression analysis, the value of regression coefficient was found to be 0.998, which showed linear relationship between concentration and absorbance.

Drug-excipient compatibility studies

FT-IR spectra showed all the characteristic peaks of promethazine HCl and the same were retained in the further samples of physical mixture.(Figure. 1) This eliminates the chance of any chemical interaction. Characteristic peaks of Promethazine HCl were retained in all the spectra. Further investigation was carried out using DSC, where drug alone with excipients and a placebo mix was analyzed. The DSC thermograms of samples were evaluated. Even though slight variation of melting range is observed, no adverse interactions that affect the drug stability are identified. The characteristic peaks of drug melting had retained in the mixture. (Figure. 2) Hence the drug may be compatible with the excipients.

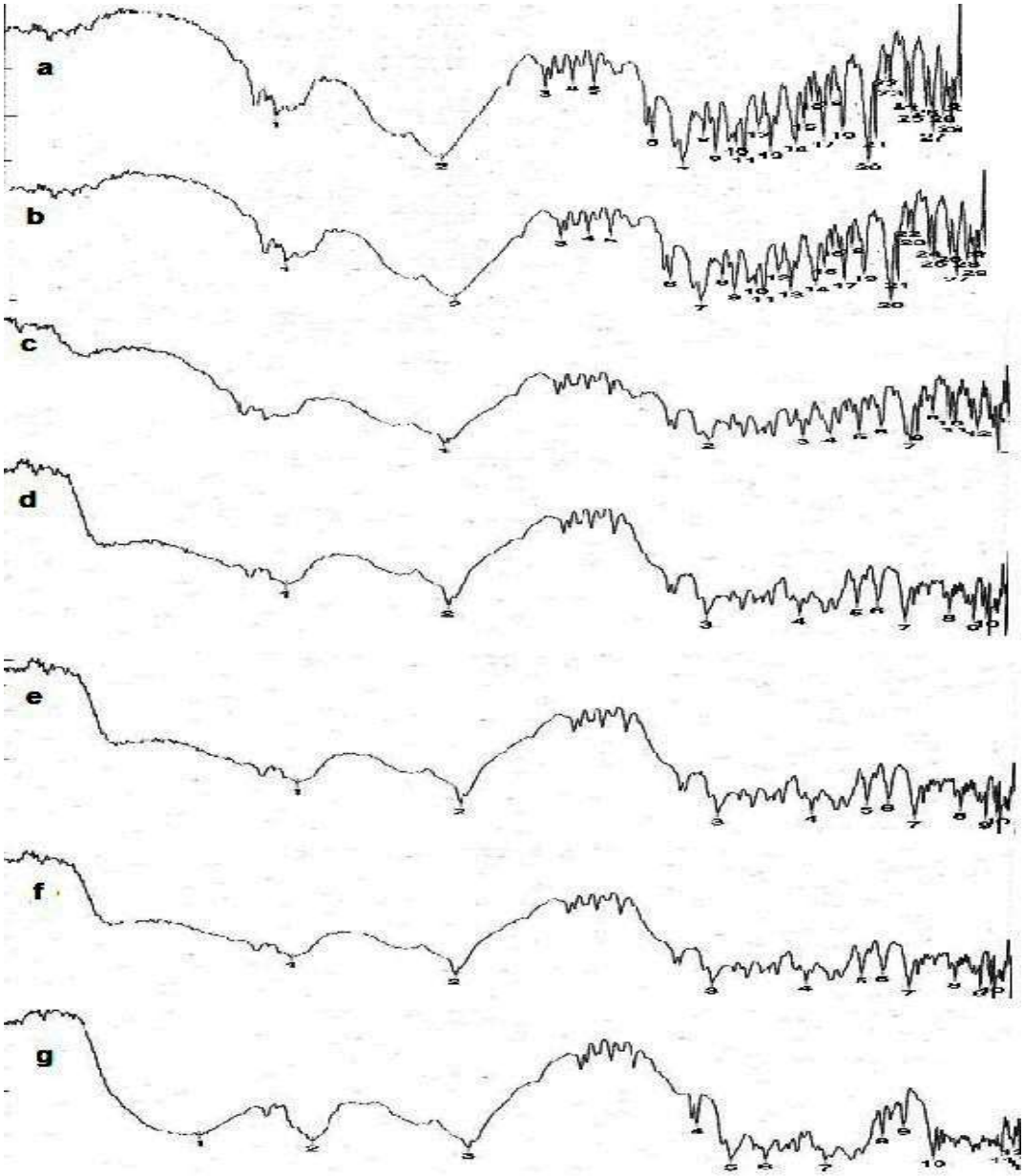

Figure 1. IR spectrum of a) promethazine HCl and promethazine HCl with b) CP (c) CCS (d) SSG (e) Dicalcium phosphate (f) Mannitol (g) MCC

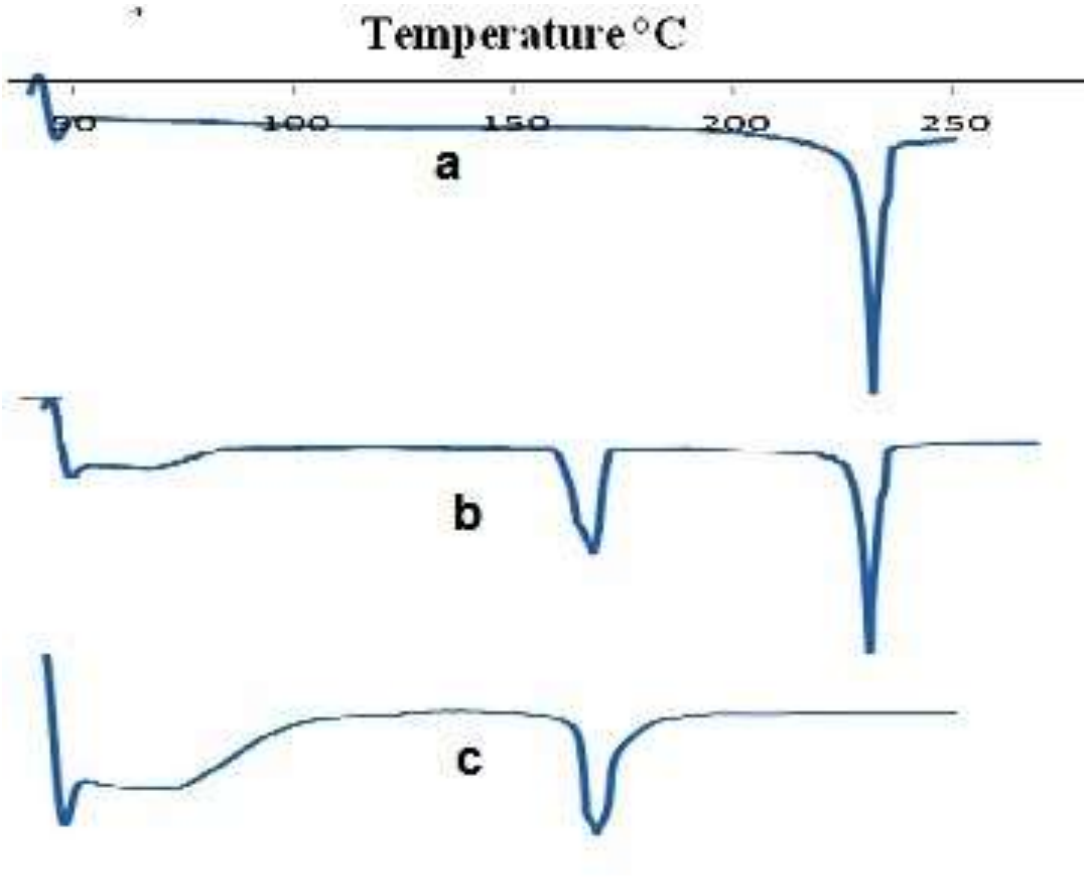

Figure. 2: DSC thermograms of (a) promethazine HCl (b) MDT (c) placebo MDT

Evaluation of preformulation parameters

Angle of repose, Carr's index values etc. indicates satisfactory to good flow of powder mix, which is suitable for direct compression. The result of angle of repose was ranged between 26.81 and 32.84 which indicate good flow properties of powder, which may be suitable for direct compression.

Evaluation of physico-chemical parameters of developed formulations

Hardness, thickness, friabiliy weight variation, drug content uniformity etc. of tablets were evaluated and the results are given in table 2.

The formulation which showed the less DT has a hardness of 3.25±0.05 (F14) which may be sufficient for blister / strip packings. All the formulations showed friability below 1%w/w which fulfilled the official requirements of IP. It was observed that as there is decrease in the friability while increase in the hardness of the tablets. So, hardness was increased to reduce the friability and the concentration of the disintegrating agent was also increased for the rapid disintegration time. The average wetting time of all the formulations was obtained in the range of 21±0.5 to 231±2.1

sec. The maximum wetting time of 231±2.1 sec which showed by formulation F31 and the minimum wetting time was shown by formulation F14 21±0.5 sec. Crospovidone formulation showed faster wetting time then other formulation. The increasing the concentration of inorganic substance DCP increase wetting time and hence increased the DT. *In-vitro* disintegration time of all the seventeen formulation varied from 17±0.5 to 216±3 S (Figure 3). DT decreased with increase in super disintegrant level The *in-vitro* disintegration time was rapid in formulations containing crospovidone as compare to the formulations containing croscarmellose sodium and sodium starch glycolate. This is due to rapid up-take of water from the medium, swelling and bursting effect. It was also noticed that as the disintegrants concentration was increased from 4 to 10 %, the time taken for the disintegration time was reduced. The formulation F14 is the best formulation, as it showed least disintegration time 17±0.5S. The *in vitro* dispersion pattern of F14 formulation is shown in the figure 4.

Table 2: Physico-chemical parameters of developed mouth dissolving tablet formulations

Formulation code	Hardness (kg/cm^2)	Friability(% loss)	Weight variation (mg)	Uniformity of drug content (%)	Thickness (mm)	Wetting Time (sec)	Disintegration time(sec)
F11	3.43 ± 0.06	0.3	128.58 ± 2.35	99.24 ± 1.28	3.4 ± 0.04	94 ± 0.5	61 ± 1.0
F12	3.16 ± 0.07	0.46	129.67 ± 2.02	99.42 ± 1.09	3.1 ± 0.04	63 ± 1.2	38 ± 1.0
F13	3.19 ± 0.05	0.3	128.69 ± 2.12	99.07 ± 2.19	3.2 ± 0.03	44 ± 0.30	26 ± 2.0
F14	3.25 ± 0.05	0.38	130.2 ± 2.25	98.82 ± 0.29	3.1 ± 0.06	21 ± 0.5	17 ± 0.5
F21	3.06 ± 0.10	0.4	131.98 ± 1.70	98.31 ± 0.86	3.3 ± 0.03	110 ± 0.5	104 ± 0.5
F22	2.94 ± 0.04	0.3	129.8 ± 1.65	97.25 ± 0.53	3.4 ± 0.04	100 ± 2.2	88 ± 1.5
F23	2.90 ± 0.05	0.46	130.42 ± 1.60	100.69 ± 1.46	3.1 ± 0.05	65 ± 0.5	73 ± 1.0
F31	3.58 ± 0.03	0.51	129.03 ± 1.89	101.2 ± 0.31	3.5 ± 0.08	231 ± 2.1	216 ± 3
F32	3.43 ± 0.07	0.23	131.5 ± 1.07	100.03 ± 1.14	3.2 ± 0.04	120 ± 1.5	99 ± 2.5
F33	3.16 ± 0.09	0.38	129.05 ± 1.92	99.09 ± 0.02	3.3 ± 0.1	99 ± 0.5	80 ± 2.0
F41	2.97 ± 0.08	0.61	130.21 ± 2.19	100.0 ± 0.05	3.6 ± 0.01	28 ± 0.5	18 ± 1.5
F42	2.79 ± 0.05	0.69	128.6 ± 1.75	98.92 ± 1.23	3.1 ± 0.05	31 ± 1.0	17 ± 1.0
F43	3.01 ± 0.03	0.77	130.5 ± 1.56	98.62 ± 1.78	3.5 ± 0.03	36 ± 1.5	27 ± 1.0
F51	2.98 ± 0.08	0.85	131.05 ± 1.05	100.04 ± 0.05	3.3 ± 0.02	48 ± 2.0	27 ± 0.5
F52	3.15 ± 0.02	0.77	129.9 ± 2.05	101.01 ± 0.02	3.4 ± 0.05	45 ± 1.5	24 ± 1.5
F53	3.05 ± 0.07	0.69	130.3 ± 1.03	99.87 ± 1.02	3.1 ± 0.1	42 ± 1.0	22 ± 1.5
F54	2.79 ± 0.03	0.84	131.03 ± 1.20	101.15 ± 0.07	3.2 ± 0.03	40 ± 0.5	22 ± 0.5

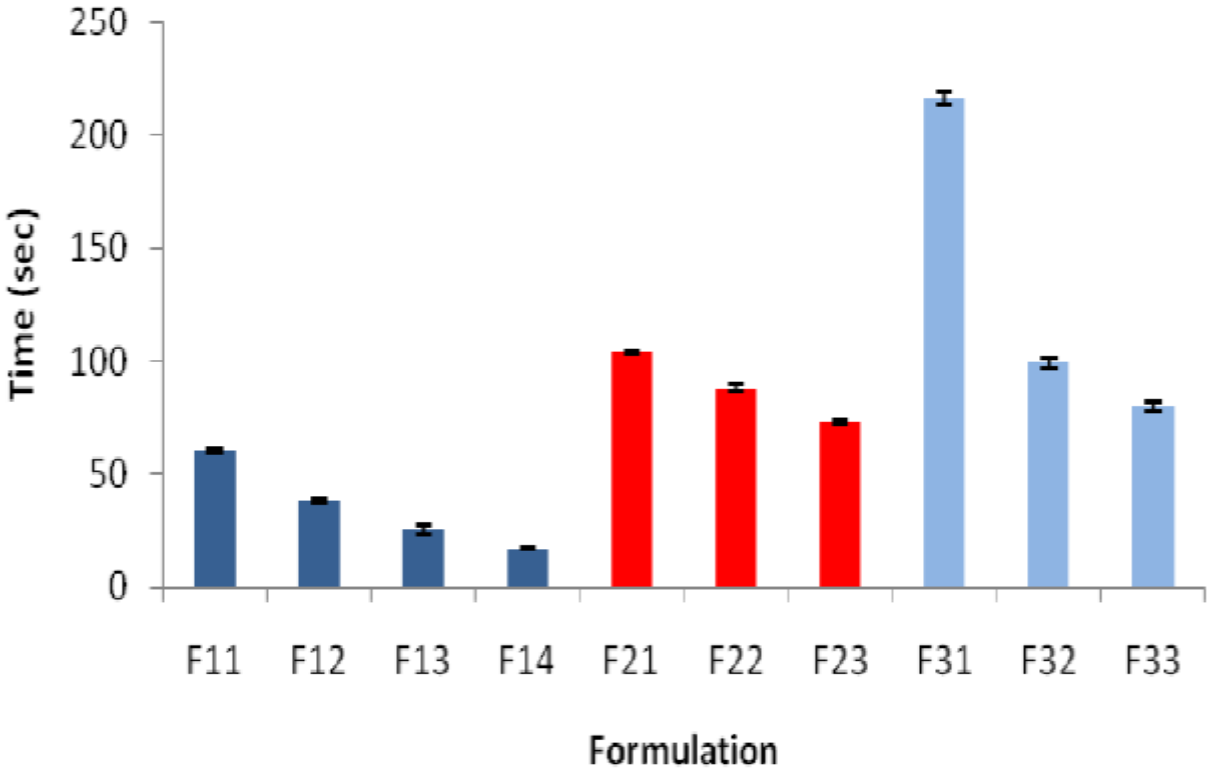

Figure 3: *In vitro* dispersion time of promethazine HCl mouth dissolving tablets

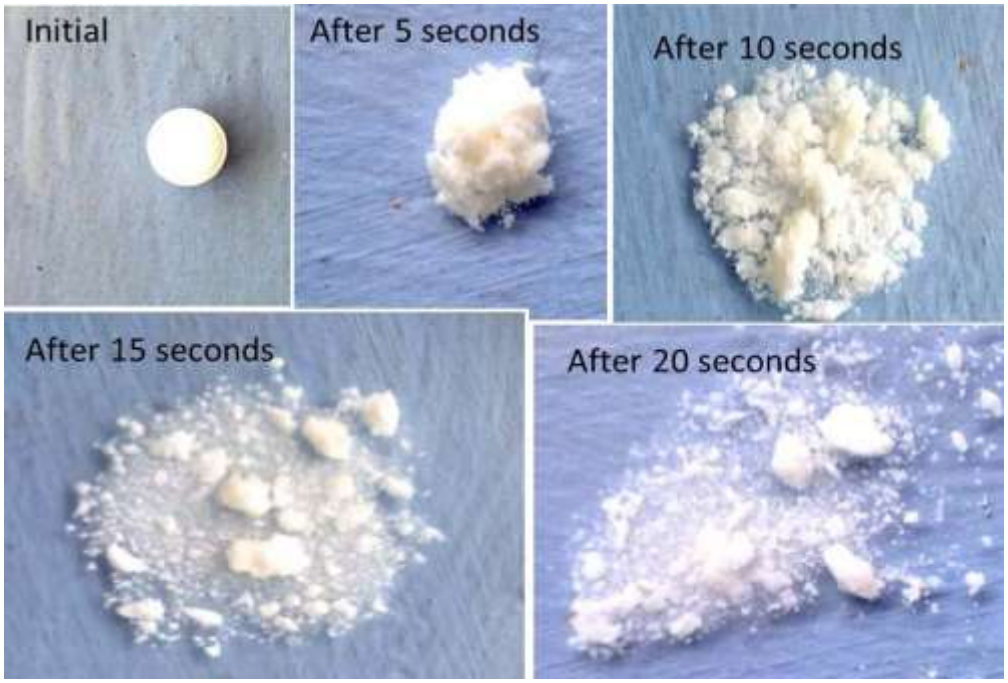

Figure 4: *In vitro* dispersion of F14 batch tablets at various times in buffer solution

***In-vitro* drug release studies**

The release of promethazine hydrochloride from mouth disintegrating tablets varied according to the proportions of various super disintegrants. After 5 min dissolution studies for formulations F11

to F54, the drug release varies from 25.33 ± 3.72 to 99.62 ± 0.51%. Crospovidone based formulations showed an increase in the drug release with gradual increase in crospovidone content. Sodium starch glycolate based formulations showed an increase in the drug release with gradual increase in sodium starch glycolate content. Croscarmellose sodium based formulations showed the progressive increase in the drug release with gradual increase in croscarmellose sodium content (Figure 5). The in-vitro drug release results represents, crospovidone based formulation F14 is the best, as it showed maximum drug release more than 90% within 1 min and almost 99.62% in 5 min, among the formulations.

Addition of inorganic material does not show any significan effect on drug release pattern of selected formuation, while lactose decreased the rate of drug release (Figure 6). It can be justified as the time taken for lactose to dissolve makes the drug release slower where as DCP does not interact with aqeous solutions.

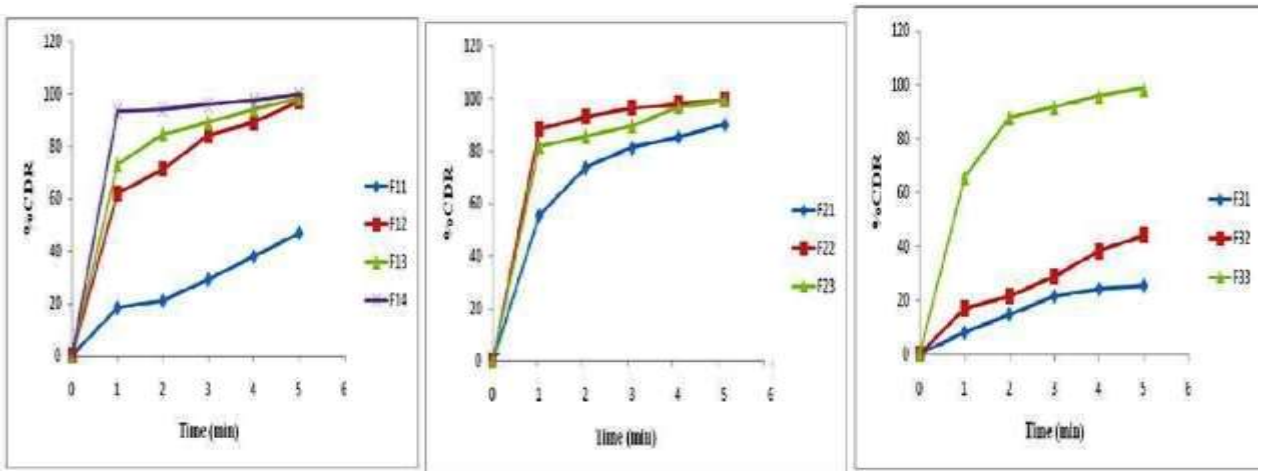

Figure 5: *In vitro* dissolution of formulations containing various super disintegrants

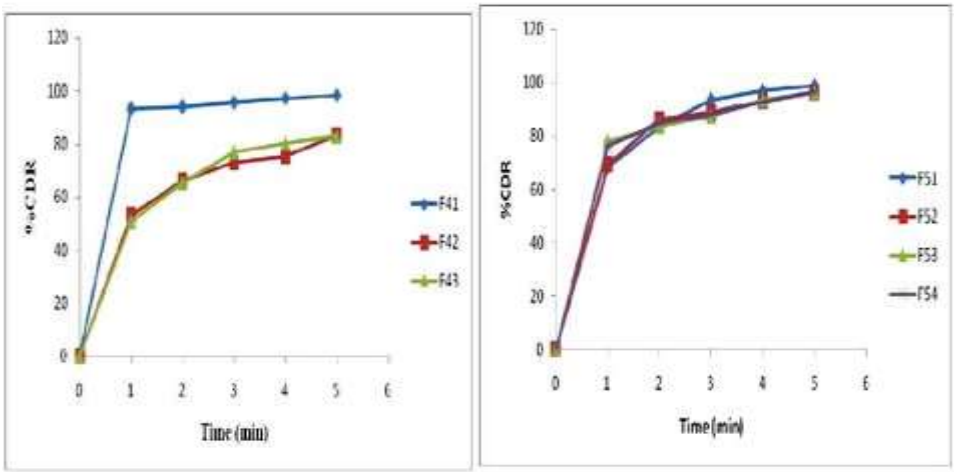

Figure 6: *In vitro* dissolution of formulations containing DCP and lactose

Stability studies

Stability studies were carried out on the most satisfactory formulation F14 at 30 ± 2°C/65 ± 5% RH and 40 ± 2°C/75 ± 5% RH for two months to assess their long term stability as per ICH guidelines. At various time intervals of 30 and 60 days, samples were evaluated for their physico chemical properties. There was no major change in the various physicochemical parameters evaluated like hardness, drug content, *in vitro* dispersion time and *in vitro* drug release pattern at the various sampling points. (Table 3) There was no significant difference between the initial values and the results obtained during stability studies indicating that the formulation may be stable in ambient conditions for longer periods.

Table 3: Stability studies of Promethazine HCl fast dissolving tablets

Evaluation Parameters	Stored at 30±2°C 65±5%RH		Stored at 40±2°C 75±5%RH	
	After 30 days	After 60 days	After 30 days	After 60 days
In vitro dispersion Time(s)	23	27	26	35
Hardness(kg/cm^2)	3.1	3.1	3.1	3
Drug content (%)	98.2	97.7	98.3	97.32

CONCLUSION

In the present study, the feasibility for direct compression of powder mix of promethazine hydrochloride and excipients was evaluated. All the batches showed good to satisfactory free flowing properties which made it suitable for direct compression. FT-IR and DSC studies proved that superdisintegrants and all the other ingredients are compatible with promethazine hydrochloride. It was concluded that promethazine can be formulated as fast dissolving tablets using crospovidone as a super disintegrant at a concentration of 4 to 10%w/w. It was found that the increases the solubility of promethazine in fast dissolving tablets. The formulated fast dissolving tablets of promethazine hydrochloride may be useful for motion sickness, nausea or vomiting and antihistamine, which can improve the patient compliance and hence can minimize the premature therapeutic dropouts leading to better therapeutic efficacy.

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