Nat. Volatiles & Essent. Oils, 2021; 8(5): 1873 - 1883

NVEO
Natural Volatiles & Essential Oils

A Comparative *In-Vitro* Dissolution And *In-Vivo* Bioavailability Study Of Mouth Dissolving Film Of Promethazine Hydrochloride Against The Marketed Tablet Formulation

Jyoti Vardhan Jaiswal*[1], Rajendra Pal Singh Rathore[1], Mridul Ranajan[2] And Piumitali Bera[3]

[1]*Department of Pharmaceutics, B.N.College of Pharmacy,Udaipur, Rajasthan-313001, India.*
[2] *Institute of Medical Sciences, BHU, Varanasi, Uttar Pradesh-221005, India*
[3]*Alkem Research Center, Navi Mumbai, Maharashtra- 410208, India*

ABSTRACT

Objective: Aim of this study is to compare the in-vitro multimedia dissolution and in-vivo bioavailability of mouth dissolving film of Promethazine hydrochloride with marketed tablet formulation.

Method: Solvent casting method was used to prepare the mouth dissolving film. The prepared film was characterized for average weight, thickness, drug contents, mechanical properties and disintegration time. Multimedia dissolution comparison of the film was performed in 0.01N Hydrochloric acid, pH 4.5 acetate buffer and pH 6.8 phosphate buffer to calculate the f2 values in each media. Furthermore, the film was evaluated for bioavailability comparison with the marketed tablet formulation Phenergen-10 in New Zealand male albino rabbits.

Results: Value of similarity factor (f2 value) was found more than 50%, in all three dissolution media. There was no statistically significant difference found between the pharmacokinetics parameters; Cmax, AUC_{0-t} and $AUC_{0-\infty}$. The 90% CI values for the mean ratios (test/reference) of C_{max} (112.245 ng/ml), AUC_{0-t} (106.451 ng/ml.hr) and $AUC_{0-\infty}$ (104.067 ng/ml.hr) suggested that the test formulation is bio-equivalent to the reference tablets.

Conclusion: These findings revealed that the mouth dissolving film of promethazine hydrochloride could be the promising option of the conventional tablet formulation for controlling the motion sickness in elderly and giardiac population.

Keywords: Multimedia Dissolution, Mouth dissolving film, Bio-equivalence study, Promethazine hydrochloride

INTRODUCTION

Many geriatric and pediatric patients feel difficulty in swallowing solid dosage forms like tablets or capsules [1]. Therefore, ease of delivery of dosage forms is of paramount importance, especially in emesis like conditions where patients find difficult to gulp the tablets or capsules; In recent years, orally disintegrating drug delivery system have been developed to resolve these issues. Orally disintegrating tablet (ODT) is an example of this type of drug delivery system, is a solid dosage form that is placed in the oral cavity and allowed to disperse in the mouth before swallowing. But ODT products are fragile and friable. On the other hand, mouth dissolving film resolves this type of issue. This novel type of dosage form is the thin film of polymer which dissolves rapidly when placed on the tongue which ultimately leads to improved patient compliance.

Nausea and vomiting are the pathophysiological conditions which may be the results of various situations like motion, chemotherapy, pregnancy, and postoperative conditions. Promethazine

hydrochloride is a phenothiazine derivative which is first generation anti-histamine with strong sedative effect [2]. It has histamine receptor (H1 receptor) blocking properties with some extent of dopamine receptor blocking activity. In addition to anti histamine it is also therapeutically effective as an anti-emetic in certain conditions like motion sickness and pre and post-operative conditions [3]. Patients need quick relief during motion sickness. So, the mouth dissolving film formulation of promethazine hydrochloride may be useful in this type of situations especially in pediatric and elderly patients. Being a BCS class 1 molecule, it is very suitable candidate to be formulated as mouth dissolving film [4].

MATERIAL AND METHODS

Materials

Promethazine hydrochloride was procured from by Sigma Aldrich, Mumbai, India; HPMC E-5 was gift sample form Colorcon, Asia, Goa, India; Polyethylene glycol-400 was received as gift sample from BASF, Mumbai; Tween-80 was purchased from the Vashudha Chemicals, Navi Mumbai. Sucralose was gift sample from Advance Inorganics, Delhi, India; Citric acid monohydrate was purchased from the Canton Laboratory, Vadodara, India; Powder Lemon Flavour was gift sample from the Bell Flavours, Mumbai, India; Colour sunset yellow was procured as gift sample by the Roha Dye chem Pvt. Ltd, Mumbai, India.

Preparation of the film

Solvent casting method was used to prepare the fast dissolving oral films [5]. Film was prepared in two steps process I. Preparation of polymeric solution and II. Preparation of drug solution. Polymeric solution was prepared by dissolving HPMC E-5, PEG-400 in purified water under stirring. Drug solution was prepared by dissolving Promethazine hydrochloride in purified water followed by the addition of the drug solution in polymeric solution under constant stirring. Finally, add other remaining excipients Tween-80, Citric acid monohydrate, Colour sunset yellow supra, Flavour Lemon one by one in the above solution under stirring at 1200 rpm to get clear viscous liquid. Prepared solution was kept under stirring at 150 rpm to remove all the entrapped air from the solution. This viscous liquid was then casted on the glass petri dish followed by drying at selected temperature for overnight. After the film dried, it was carefully removed from the petri dish and cut in to 2 X 1 cm^2 of rectangular shape films. Wrap each film with aluminum foil to store the prepared films.

Optimization of the films

Selection of the components and their level for the film preparation

Various film forming polymers such as, Sodium carboxy methyl cellulose, HPMC E-15 and HPMC E-5 were tried to formulate the suitable mouth dissolving films. Film prepared with Sodium Carboxy methyl cellulose did not show good mechanical properties, whereas films of HPMC E-15 showed good mechanical properties but with higher disintegration time. Films of HPMC E-5 pass all the preliminary criteria for the formation of the desired mouth dissolving film. The level of independent variables of the film was optimized by using four factor three level Box behnken experimental design.

Characterization of the mouth dissolving film

The prepared film was characterized for the following parameters:

Average weight and Uniformity of weight

Six randomly selected films were weighed individually on the digital weighing balance and determine the average weight of the films.

Thickness

Film thickness (n=6) was measured by vernier calipers. Thickness was measured at four corners and at the middle of the film. The average of the five readings is the film thickness.

Drug Content

Powder the 20 films in pastel mortar. Transferred the powdered contents equivalent to 50mg of Promethazine hydrochloride in 10 ml of 2M hydrochloric acid added 200 ml of water and shaken for 15 minutes. Make up the volume up to 500 ml with water. Centrifuge the 50 ml of the mixture. Added 10 ml of 0.1N hydrochloric acid to 5 ml of the clear supernatant liquid, followed by addition of sufficient water to produce 100 ml. Determined the contents of Promethazine hydrochloride in the resultant solution by measuring the absorbance in UV spectrophotometer at wavelength maximum of 249 nm [6].

Mechanical property

Mechanical properties of the films were determined by using Ametek LS1 (Make: Lloyd). The film was clamped between the upper and lower gauze of the instrument with 10mm distance apart. Two gauzes were set to move away in the opposite direction at cross head speed of 5 mm/min creating a stress on the film. Three parameters i.e.; i) Tensile strength, ii) Percent Elongation and iii) Young modulus were determined following the breakage of the film [7].

Disintegration time

Disintegration time of the film was determined placing the film on the surface of 2 ml distilled water filled in petri dish and disintegration time was recorded when the film completely disintegrated. Disintegration time was performed on the six films individually [8, 9].

Multipoint and multimedia dissolution comparison with the marketed tablet formulation (Similarity factor; f2 value)

The similarity factor (f2 value) approach is used to demonstrate the similarity in dissolution profile between test and reference products. This is mathematical model used to predict the sameness of the test product with the reference product with respect to their in vivo behavior. The value between 50-100, favors similarity between the products [10, 11]. Similarity factor assessment is done by performing the dissolution profiling of test product against the reference product. At least, three dissolution medium including validated one as described in the compendial monographs to be used to execute the f2 test. The experiment is to be carry out on 12 units of each test and reference product in identical conditions with same time points with samples; e.g. 5 mins, 10 mins ,15 mins, 20 mins, 30 mins and so on till at least 90% dissolution not achieved. The mean dissolution data at each

time point is used to calculate the f2 value where, % coefficient of variation should not be more than 20% at the initial time point and not more than 10% thereafter.

Mathematical formula for f2 calculation: Formula for the similarity factor (f2) mentioned in below equation.

$$f2 = 50 \times log10\left\{\left[1 + \frac{1}{N}\sum(Rt - Tt)^2\right]^{0.5} \times 100\right\} \quad \text{(i)}$$

Where,

N= Total numbers of time points

Rt= Percent dissolution of reference product at time t,

Tt= Percent dissolution of test product at time t,

Method: Optimized test product was evaluated for the dissolution similarity against the reference marketed product Phenergan-10 Tablets. Twelve units of both test and reference were tested in three dissolution medium i.e. 1.) 0.01 N Hydrochloric acid, 2.) pH 4.5 acetate buffer and 3.) Simulated salivary media of pH 6.8 phosphate buffer. Volume and paddle speed was 900 ml and 75 RPM respectively. The time points for sample collection were 0 mins, 5 mins, 10 mins, 15 mins, 20 mins and 30 mins. Each time 2 ml volume was withdrawn and equal volume of fresh media was added to maintain the sink condition each time. Pooled samples were spectrophtometrically examined for dissolved promethazine hydrochloride for both test and reference product at each time points.

In-vivo animal study [12]

Experimental animals: The optimized film formulation was further selected for the in-vivo animal study for its effectiveness against the innovator product Phenergan-10 containing Promethazine hydrochloride. All the procedure used in animal study was approved by the committee for the purpose of control and supervision of experiments on Animals (CPCSEA). Six healthy male New Zealand white rabbits with mean weight of 2.68kg (± 0.222) were selected for the study.

Study Design: A randomized, open label, balanced, two treatments, two periods, two sequences, single oral administration, cross over, two weeks wash out period, comparative bioavailability study in healthy adult male New Zealand rabbits.

Ethical Consideration: The conduct of animal study was approved by the Institutional animal ethics committee (IAEC) with the approval no. DL/IAEC/32/2020 and CPCSEA approved no. 1410/C/11/CPCSEA.

Experimental condition: All animal were confined within the facility for at least 24.00 hrs under 12/12 hrs dark/light cycle with free access to food and water prior to start of the experiment during each study period. Room of animals was equipped with temperature control of 25^{o}C ± 1^{o}C and relative humidity of 60% RH ± 5% RH. Rabbits were fasted overnight at least 10.00 hrs before dosing but had free access to water *ad libitum*. Animals were divided in two groups with three rabbits in each (Group1 and Group 2).

Experiment: Animal group receiving test formulation was anaesthetized with I.V. injection of 25mg/kg phenobarbitan and placed on a table with the lower jaw in a horizontal supported position and ODF was kept carefully on the tongue of the rabbits. Anesthesia was given to the rabbits in

order to ensure maintenance of the mouth dissolving film on tongue without clear out from the oral cavity. Reference product (Phenergan-10) was administered orally through gastric lavage.

Blood sample Collection: Blood samples (2 ml per sample) were collected from animal's marginal ear vein in pre-labelled heparinized glass tube at immediately before drug formulation and at 15 mins, 30 mins, 45 mins, 60 mins, 1.50 hrs, 2 hrs, 3 hrs, 4 hrs, 5 hrs, 6 hrs, 7 hrs, 8 hrs, 10 hrs, 12 hrs, 18 hrs, 24 hrs and 36 hrs post dose within 2 minutes of schedule sampling time.

The collected blood samples were centrifuged under refrigeration with the machine set at 3500 RPM, 5 minutes and at 5^{o}C ± 3^{o}C. The separated plasma from blood was transferred to appropriate size polypropylene vials in duplicate and stored at -20^{o}C ± 10^{o}C in deep freezer.

Pharmacokinetic Parameters: The pharmacokinetic parameters were calculated by non-compartmental method using SAS software. Primary Pharmacokinetic parameters viz. 1. Peak plasma concentration (cmax), 2. Area under the plasma concentration time curve from 0 hrs to the last measurable concentration (AUC_{0-t}) 3. Area under the plasma concentration time curve up to infivnity ($AUC_{0-\infty}$) and Secondary pharmacokinetic parameters viz., 1. Time to reach peak plasma concentration (T_{max}), 2. Elimination rate constant (K_{el}) 3. Elimination half life ($t_{1/2}$) were estimated for each given test and standard marketed formulation.

Determination of Promethazine hydrochloride by HPLC[13]

Extraction of Promethazine hydrochloride from plasma and Preparation of test solution: 0.5 ml of plasma added to 100 µl of 1N sodium hydroxide, 1.5 ml ter-butyl ethyl ether. Tubes were allowed to centrifuge at 1500X for 3 mins. The organic part was shifted to a conical tube and dries it in a water bath at 40^{o}C. Obtained residue was dissolved with 100 µl of mobile phase followed by 20µl injected to the HPLC system.

HPLC System: The HPLC system (Agilent, model 1260) consisted of a solvent pump, injection valve, pre-column, Inertsil ODS 250 mm X 4.6 mm, 5 micron column and a UV detector of 250 nm wavelengths. Mobile phase comprised of pH 5.6 Sodium dihydrogen Orthophosphate:Acetonitrile: Methanol (500:300:200). Sample injection was 20µl with flow rate and run time of 1.0 ml/min and 20 minutes respectively.

Standard stock preparation: Promethazine hydrochloride in water and Acetonitrile (7:3 v/v) to prepare 1mg/ml concentration. This solution was successively diluted with water and mixed with plain plasma to attain working standard of concentration 1, 5, 10, 25, 50, 100, 200 and 300ng/ml. The calibration curve was drawn by linear regression of prepared drug concentration.

RESULTS AND DISCUSSION

Selection of the components and their level for the film preparation

HPMC E-5, PEG-400 and Tween-80 were selected as main functional components to formulate the mouth dissolving film based on initial preliminary screening of the components. Concentrations of these components were optimized by using the software design expert (version no. 12.0.3.0). A box-behnken design was employed for response surface methodology with no blocks. Total 29 trials were suggested by the software and each trial was prepared and evaluated to find out the best optimized composition of the film. The values of evaluation parameters of each trial were entered in the software. The optimized concentration of 12.72%, 9.99% and 0.54% of HPMC E-5, PEG-400 and

tween-80 respectively, was suggested by the software with the 50°C drying temperature to formulate the mouth dissolving film of promethazine hydrochloride. The composition of mouth dissolving film of promethazine hydrochloride is shown in table 1.

Table 1: Composition of the mouth dissolving film of Promethazine hydrochloride

Components of the films	Quantity (% w/w)
Promethazine hydrochloride	4.2%
HPMC E-5	12.72%
PEG-400	9.99%
Tween-80	0.54%
Citric acid	0.1%
Sucralose	0.1%
Colour Sunset yellow Supra	0.01%
Flavour Lemon	0.1%
Purified water	q.s.

Characterization of the film formulation

Average weight: Results of film weight are shown in table 2. Low value of standard deviation suggests the prepared films were uniform in weight.

Thickness: The average value of film thickness was 169.33 µm (table 2). Very low value of standard deviation revealed that the prepared film was uniform in thickness.

Drug contents: Drug content of the film was recorded at 99.55%. Very low value of standard deviation indicates the uniformity in the distribution of drug throughout the film.

Mechanical Properties: values of mechanical properties of the film were shown in table 2. Mechanical properties of the film were recorded in the form of tensile strength, percent elongation and young modulus with the values of 22.347 ± 0.320, 11.628 ±0.310 and 235.159 ±10.294 respectively. The results are given in table 2. Values of mechanical parameters indicated that the prepared film is very firm and flexible.

Disintegration time: Prepared film was disintegrated in 53 seconds. Disintegration time less than 60 seconds is desired for the ideal mouth dissolving film. Results of disintegration time of the oral film of promethazine hydrochloride shown in table 2.

Table 2: Characterization of the film

Parameters	Results
Weight/UOW (mg)	71.80±0.182
Thickness (µm)	169.33±7.40

Drug Content (%w/w)	99.55±0.413
Tensile strength (kgf/Cm^2)	22.347 ± 0.320
% elongation (%)	11.628 ±0.310
Young modulus (kgf/Cm^2)	235.159 ±10.294
Disintegration time (S)	53.0 ±1.471

Data are expressed as mean±SD; n=6, where mg= milligram, µm = micrometer, %w/w = percent weight/weight, Kgf/Cm2= kilogram force per centimeter square, %= percent, S= seconds, SD= Standard deviation

Multimedia dissolution comparison with marketed reference product

Result of f2 values in all three media i.e. 0.01 N hydrochloric acid, pH 4.5 Acetate buffer and pH simulated salivary media of pH 6.8 phosphate buffer is presented in table 3 with their mean dissolution value ± SD and % CV values. All the mean dissolution values were passed the criteria of % CV value less than 20% for the initial time point and below 10% CV for subsequent time points. Highest dissolution of the drug was observed with the simulated salivary media of pH 6.8 phosphate buffer with 93.36 ±1.14% in 15 minutes for oral film formulation against the 85.36 ±1.25% dissolution in 15 minutes in case of reference drug Phenergan-10 Tablets. Similarity in results of the in vitro dissolution tests in all selected dissolution media was validated by f2 value with 50<f2<100indicated similar pattern of dissolution of both products. Both the Promethazine hydrochloride oral films and Phenergan-10 reference drug dissolving completely by more than 80% within 30 minutes in all three dissolution media indicated that the Promethazine hydrochloride oral film had comparable dissolution with reference drug Phenergan-10. Comparative dissolution profile of both film formulation and marketed tablet formulation in three selected media is depicted in in fig.1a, 1b and 1c, respectively.

Table 3: Multimedia dissolution results with similarity factors

Time point (mins)	**Statistical data**	**Percent of Promethazine hydrochloride Dissolved (n=12)**					
		0.1 N Hydrochloric acid		**pH 4.5 acetate buffer**		**pH 6.8 simulated salivary media**	
		MDF1	**Phenergan-10 Tablets**	**MDF1**	**Phenergan-10 Tablets**	**MDF1**	**Phenergan-10 Tablets**
0 min.	**Mean ± SD**	0.00	0.00	0.00	0.00	0.00	0.00
	% CV	0.00	0.00	0.00	0.00	0.00	0.00
5 mins	**Mean ± SD**	58.23 ± 1.54	47.25± 1.87	61.65± 1.53	50.03± 1.71	63.48 ± 1.40	52.35± 1.72
	% CV	2.64	3.96	2.47	3.41	2.21	3.29
10 mins	**Mean ± SD**	77.56 ± 1.96	64.19± 1.78	82.46± 1.13	68.8± 1.69	83.63± 1.18	73.84± 1.67
	% CV	2.53	2.78	1.37	2.45	1.41	2.27

15	**Mean**	**±**	87.45	74.68±	92.23±	80.46±	93.36±	85.36±
mins	**SD**		± 1.74	1.78	1.16	1.72	1.14	1.25
	% CV		1.99	2.38	1.26	2.14	1.23	1.46
20	**Mean**	**±**	92.87	86.38±	95.14±	88.17±	95.92±	91.33±
mins	**SD**		± 1.56	1.18	1.15	1.74	0.91	1.26
	% CV		1.68	1.37	1.21	1.98	0.95	1.38
30	**Mean**	**±**	96.65±	93.42±	97.23±	93.93±	98.10±	95.34±
mins	**SD**		1.49	1.31	1.1	1.21	0.79	1.15
	% CV		1.55	1.40	1.31	1.28	0.814	1.21
	F2 value		**53.05**		**53.12**		**58.54**	

Data are expressed as mean±SD; n=12.

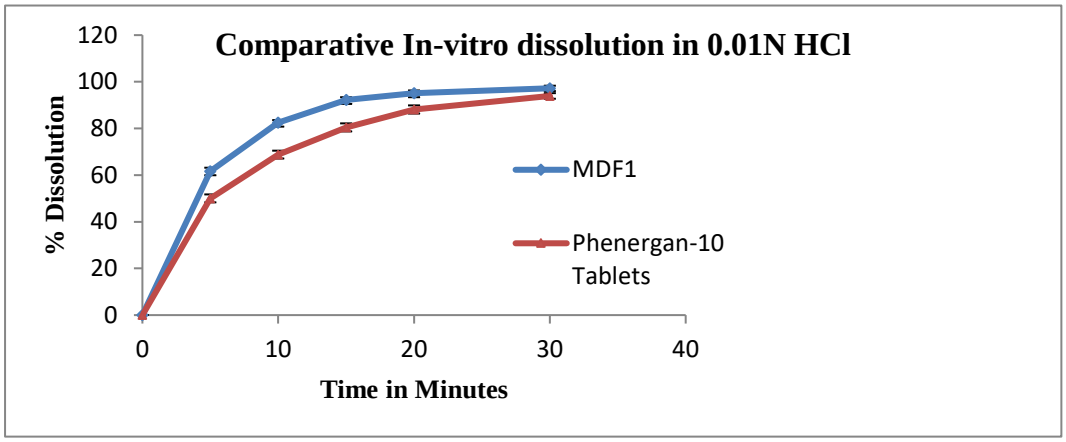

Fig.1a: Comparison of dissolution profile of mouth dissolving film of promethazine hydrochloride (MDF1) with the marketed tablet Phenergan-10 in 0.01 N HCl media.

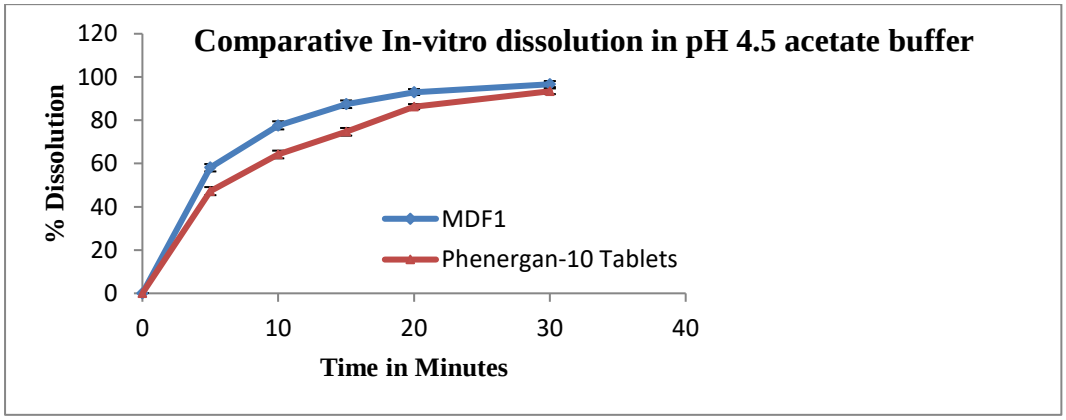

Fig.1b: Comparison of dissolution profile of mouth dissolving film of promethazine hydrochloride (MDF1) with the marketed tablet Phenergan-10 in pH 4.5 acetate buffer media.

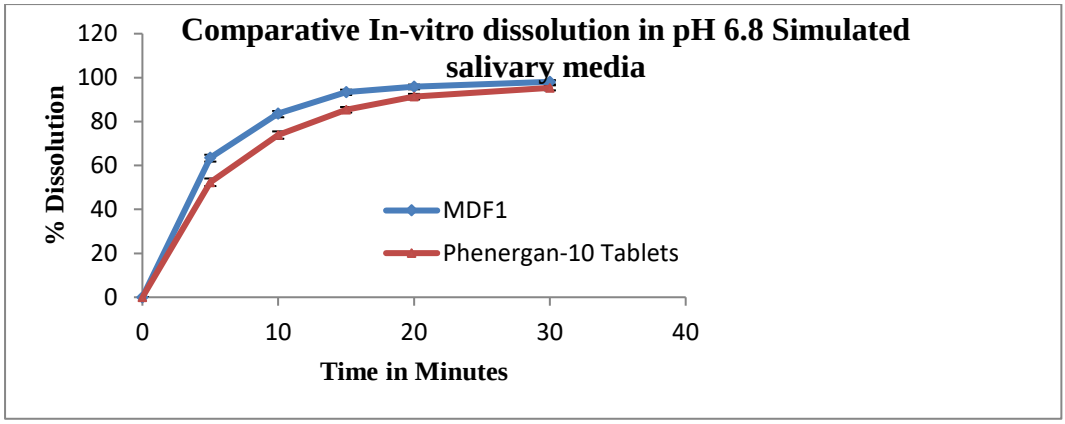

Fig.1c: Comparison of dissolution profile of mouth dissolving film of promethazine hydrochloride (MDF1) with the marketed tablet Phenergan-10 in pH 6.8 simulated salivary media.

In-vivo Pharmacokinetic studies

The pharmacokinetics data of Promethazine hydrochloride after oral administration of mouth dissolving film (MDF1) and marketed tablet formulation (Phenergan-10 Tablets) shown in table 4. After oral administration to the New Zealand male albino rabbits, the $AUC_{(0-t)}$were not significantly different (P>0.05), which indicated that both the drug formulations had similar absorption pattern in the blood. Comparison of plasma concentration time profile curve of both test and reference products was shown in Fig. 2 which presented a similar pattern of changes in drug concentration in both groups. Although, plasma concentration of Promethazine hydrochloride slightly higher in the test product with C_{max} value of 17.42 ng/ml ± 6.17 and $AUC_{(0-t)}$ 165.98 ng/ml.hr ± 51.35 with shorter peak time T_{max} 5.25 hrs.± 0.58 as comparing to reference product of Phenergan-10 Tablets.

The ratios of geometric least square mean (T/R) and its 90% confidence interval on the log transformed pharmacokinetic data C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ fall within the acceptance criteria of 80% to 125% for bioequivalence. Where, T/R ratios are 112.24%, 106.45% and 104.06% respectively. Results are tabulated in table 5.

Hence, it was concluded that the mouth dissolving film is bioequivalent with marketed product Phenergan-10 Tablets. Even though, higher C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ and shorter T_{max} observed in mouth dissolving film formulation as compared to the conventional marketed tablet formulation. The advantage of oral film formulation is the ease of administration without the intake of water which is required in certain circumstances particularly, giardiac and bed ridden patients. Who feels difficulty with swallowing the tablets or capsule dosage form.

Table 4: Pharmacokinetic data comparison of mouth dissolving film of Promethazine hydrochloride with the marketed tablet formulation Phenergan-10 in New Zealand male albino rabbits

Parameters	MDF1 (Test Product); T	Phenergan-10 Tablets (Reference Product); R
C_{max} (ng/ml)	17.422 ± 6.179	14.456 ± 6.904
$AUC_{(0-t)}$ (ng/ml.hr)	165.978 ± 51.358	161.723 ± 48.637
$AUC_{(0-\infty)}$ (ng/ml.hr)	187.318 ± 48.830	177.965 ± 52.185
T_{max} (hrs.)	5.25± 0.58	6.00 ± 1.07

Kel (hrs^{-1})	0.05 ± 0.02	0.05 ± 0.02
$T_{1/2}$ (hrs.)	12.19 ± 1.73	13.66 ± 2.46

Table 5: Geometric means and 90% confidence interval data

Parameters	Geometric mean*		% Ratio	90% CI for log transformed	
	Test (T)	Reference (R)	T/R	Lower limit	Upper limit
Cmax (ng/ml)	13.126	11.694	112.245	95.32	119.61
$AUC_{(0-t)}$ (ng/ml.hr)	160.352	150.634	106.451	97.19	112.65
$AUC_{(0-\infty)}$ (ng/ml.hr)	175.633	168.768	104.067	95.17	108.26

Where, ng/ml= nanogram per milliliter, $AUC_{(0-t)}$ = Area under the curve zero to time t, $AUC_{(0-\infty)}$ = Area under the curve zero to infinity, CI= confidence interval.

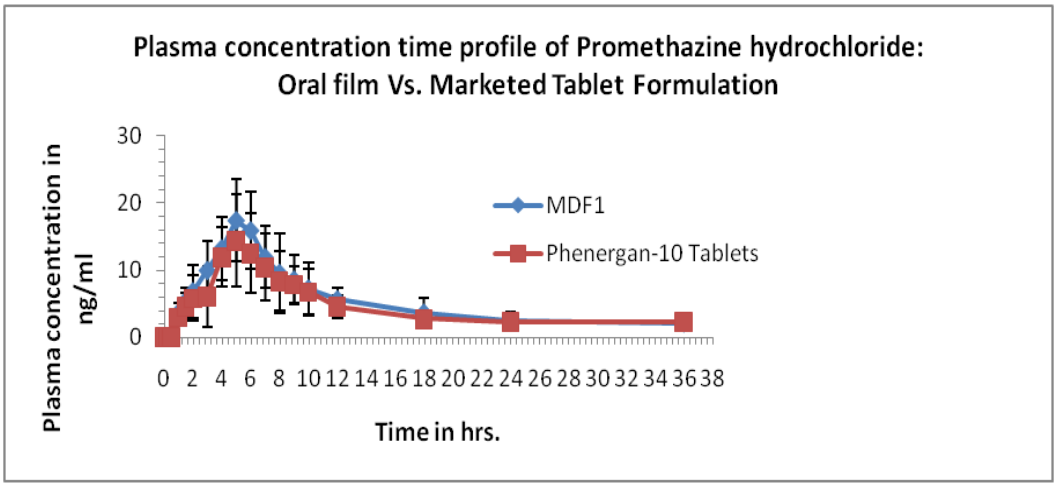

Fig.2: Promethazine hydrochloride plasma concentration-time profile with mouth dissolving film (MDF1) Vs. Marketed tablet formulation (Phenergan 10 Tablets) in New Zealand male albino Rabbits. All the data shown in mean ± SD; n=6.

CONCLUSION

Mouth dissolving film of promethazine hydrochloride could be the safe, effective and attractive alternate of the conventional tablet formulation in controlling and managing motion sickness in patients who feel difficulty in swallowing tablet or capsule dosage form.

AUTHORS CONTRIBUTION

All authors contributed in completion of this study. Jyoti Vardhan Jaiswal performed the practical work as well as writing of the manuscript. Rajendra Pal Singh Rathore helped in writing the manuscript. Mridul Ranajan helped in providing the technical support in planning the in vivo studies. All authors reviewed the manuscript.

CONFLICT OF INTERESTS

Authors have no any conflict of interests.

REFERENCES

1. Hanif M, Zaman M, Chaurasiya V. Polymers used in buccal film: a review. Des Monomers Polym. 2015 Feb 17;18: 105–11.

2. C.Cantisani, S.Ricci, T.Grieco, G.Paolino,V.Faina, E.Silvestri and S.Calvieri, Topical Promethazine side effects: Our experience and review of literature, BioMed Research International, 2013 1-10.

3. L.C.Strenkoski-Nix, J.Ermer, S.Decleene,W.Cevallos andP.R.Mayer. Pharmacokinetics of Promethazine after administration of rectal suppositories and oral syrup to healthy subjects. Am J Health-Syst Pharm.**57**(2000) 1499-05.

4. World health organization, Proposal to waive Invivo Bioequivalence requirements for the WHO model list of essential medicines Immediate release solid oral dosage forms. 2005, Rev.1; 1-45

5. D.A. El-Setouhy and N.S. Abd El-Malak, Formulation of a novel Tianeptine sodium orodispersible film, AAPS PharmSciTech. **3**(2010)1018-25.

6. Indian Pharmacoepia, Secretary, Ministry of health & family welfare, Government of India, Promethazine Hydrochloride Tablets, **18**(2018), Volume-III, 3016-7.

7. V.Garsuch andJ. Breitkreutz,Novel analytical method for the characterization of oral wafers, Eur J Pharm Biopharm.**73**(2009) 195-01.

8. E.M.Hoffman, A.Breitenbach and J. Breitkreutz, Advances in orodispersible films for drug delivery, Expert Opin. Drug Deliv. **8**(2011), 299-316.

9. V.Garsuch and J. Breitkreutz,Comparative investigations on different polymers for the preparation of fast-dissolving oral films,JPP.**62**(2010) 539-45.

10. V.P.Shah, Y. Tsong, P. Sathe and J.P. Liu, In-vitro dissolution profile Comparison-statistics and analysis of the similarity factor, f2, Pharma Research.**15**(1998) 889-96.

11. H. Saranadasa and K. Krishnamoorthy, Multivariate test for similarity of two dissolution profiles, Journal of biopharmaceutical statistics. **15**(2005) 265-78.

12. R. Bala, S. Khanna and P. Pawar, Design optimization and *invitro invivo* evaluation of orally dissolving strips of clobazam, J drug deliv. (2014)1-15.

13. E.Tanaka, T.Nakamura, M.Terada, T.Shinozuka, C.Hashimoto, K.Kurihara and K.Honda, Simple and simultaneous determination for 12 phenothiazine in human serum by reversed-phase high performance liquid chromatography, J Chromatogr B: Anal Technol Biomed. Life Sci. **854**(2007) 116-20.