ORIGINAL ARTICLE

Full factorial design, physicochemical characterization of phenylephrine HCl loaded oral thin film

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Oral dissolving drug delivery system offers a solution for those patients having difficulty in swallowing tablets/capsules. The primary objective of the present research work was to optimize oral thin film (OTF) formulation of phenylephrine HCl, a water soluble drug with three loading concentrations: High, medium and low and also to evaluate their effect on the final product attributes. The OTF was prepared by solvent casting method. All the formulations were evaluated for film forming properties, appearance, thickness, folding endurance, tensile strength, percent moisture absorption, surface morphology, *in vitro* and *in vivo* disintegration. Formulations containing low and medium loading concentration gave acceptable results while formulation with higher loading concentration resulting poor film forming properties. Hence, another objective of the present study was to investigate the effect of anti-tacking agent namely magnesium aluminum silicate (MAS), microcrystalline cellulose and colloidal silicon dioxide (CSD) by applying 2^3 full factorial design on improving the film properties of high concentration phenylephrine HCl. Formulation containing microcystalline cellulose and CSD at low level and MAS at high level was found to be suitable for film formation with desirable physicochemical properties, faster disintegration and optimum *in vitro* release.

Key words: *Anti-tacking agents, effect of variables, loading concentration, water soluble drugs*

INTRODUCTION

Route of administration of drug plays an important role in the patient compliance. Oral route is the simplest and most acceptable route. In case of oral thin film (OTF), acceptability of this dosage form is an important parameter which is a direct indication of patient compliance. Acceptability of film includes its organoleptic properties, *in vivo* disintegration, mechanical strength and percentage moisture absorption (PMA) with respect to its tackiness and stability. Looking towards market scenario most OTF formulation consists of low concentration content of drug. Since size of concentration form has its limitations that high concentration molecules are difficult to be incorporated in OTF. Generally 5% w/w to 20% w/w of active pharmaceutical ingredient can be incorporated in OTF easily.

Most commonly used method of manufacture of OTF is by solvent casting. Amongst the available film formers hydroxypropylmethyl cellulose (HPMC) is well known which is very frequently used as a coating agent in case of tablets, pellets, granules etc., HPMC has a capacity of retaining its film forming properties even in the presence of other excipients in the formulation. Vijaya *et al*.[1] has used HPMC (approximately 80%) as a polymer base for formulating montelukast sodium OTF while Lakshmi *et al*.[2] has used 18% HPMC for formulating levocitrizine hydrochloride OTF. Shaik[3] has used polyvinyl alcohol (PVA) at approximate 5% in development of Domperidone OTF.

The primary objective of the present research work was to optimize OTF formulations of phenylephrine HCl, water soluble drug with three loading concentrations: High, medium and low. Another objective of present study was to investigate the effect of anti-tacking agent namely magnesium aluminum silicate (MAS),

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microcrystalline cellulose (MCC) and colloidal silicon dioxide (CSD) by applying 2^3 full factorial design on improving film forming properties of HPMC for formulating drugs in higher loading concentration.

MATERIALS AND METHODS

Materials

Phenyephrine HCl (kindly supplied by Shilpa chemicals, India), HPMC, PVA, sucralose, bronopol, propylene glycol (PG), citric acid and lemon flavor (Kindly supplied by ZIM Laboratories Ltd., India). All other chemicals and reagents were of analytical grade.

Methods

Oral thin films of phenylephrine HCl were prepared by using solvent casting method. The formulation codes and their respective compositions are given in Table 1. An aqueous solution of HPMC and PVA was prepared

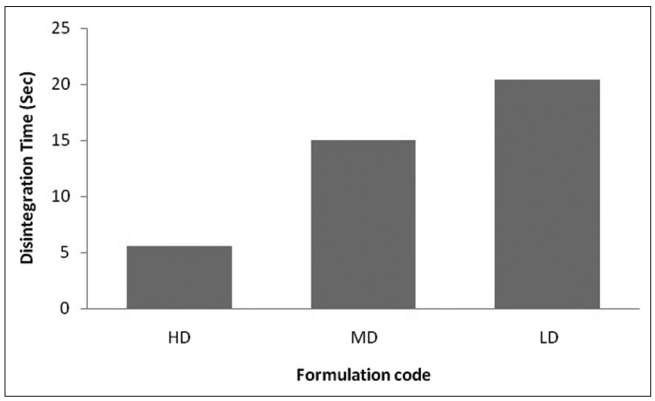


Figure 1: *In vitro* disintegration of phenylephrine HCl oral thin film

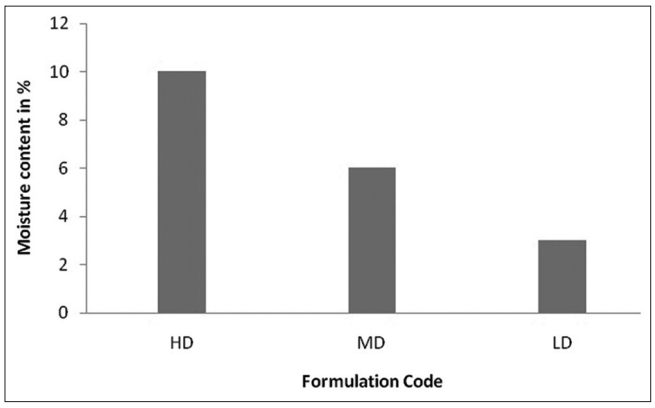


Figure 3: Tensile strength of phenylephrine HCl oral thin film

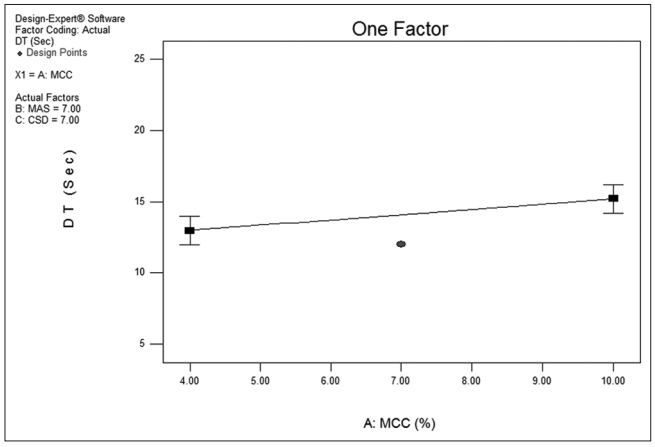


Figure 5: One-factor graphs showing effect of microcrystalline cellulose on disintegration time

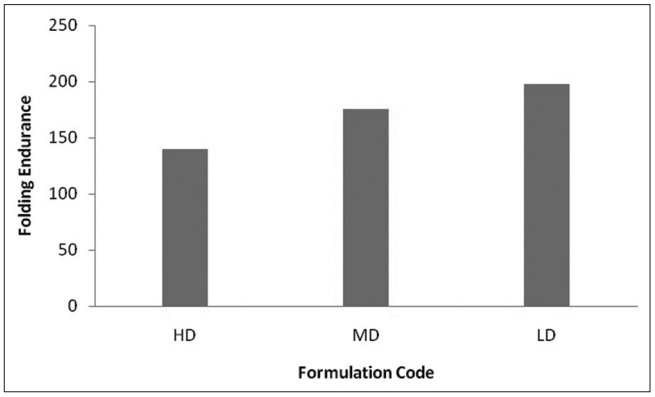


Figure 2: Folding endurance of phenylephrine HCl oral thin film

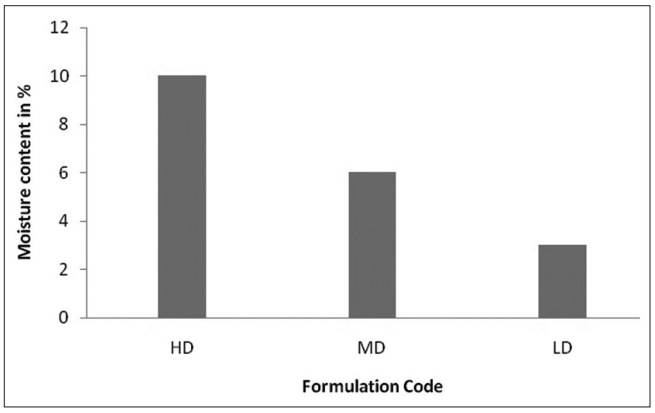


Figure 4: Percentage moisture absorption of phenylephrine HCl oral thin film

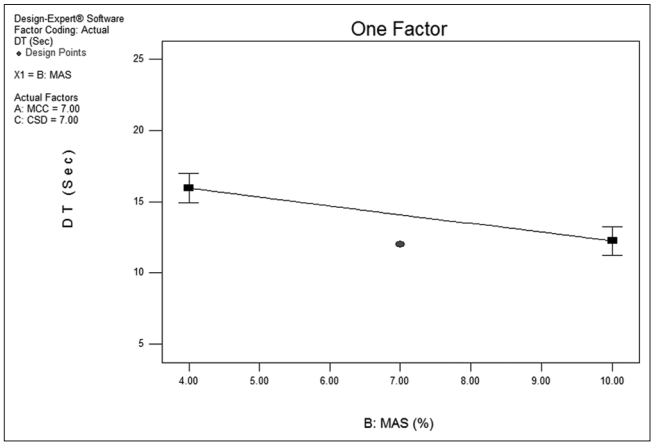


Figure 6: One-factor graphs showing effect of magnesium aluminum silicate on disintegration time

by dissolving in a fixed quantity of distilled water. To this polymeric solution measured quantities of phenylephrine HCl, sucralose, bronopol, PG, citric acid and lemon flavor were added. The suspension was stirred for 30 min. The thick viscous suspension was degassed to remove air entrapment by using ultrasonicator. Measured quantity of suspension was layered to get desirable loading with fixed wet thickness. The film was carefully removed from the glass plate, checked for any imperfections and cut to the required size. The films were stored in airtight containers for further studies.[4,5] The film samples were also stored for accelerated stability

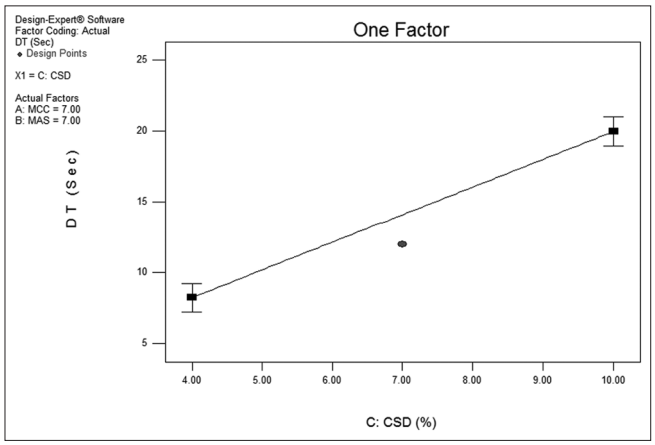


Figure 7 : One-factor graphs showing effect of colloidal silicon dioxide on disintegration time

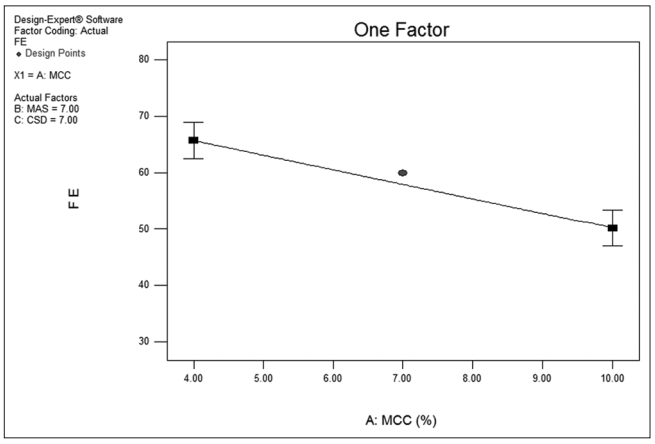


Figure 8: One-factor graphs showing effect of microcrystalline cellulose on folding endurance

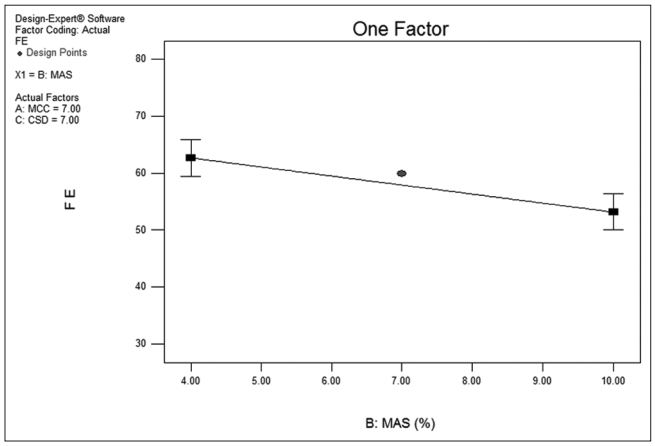


Figure 9: One-factor graphs showing effect of magnesium aluminum silicate on folding endurance

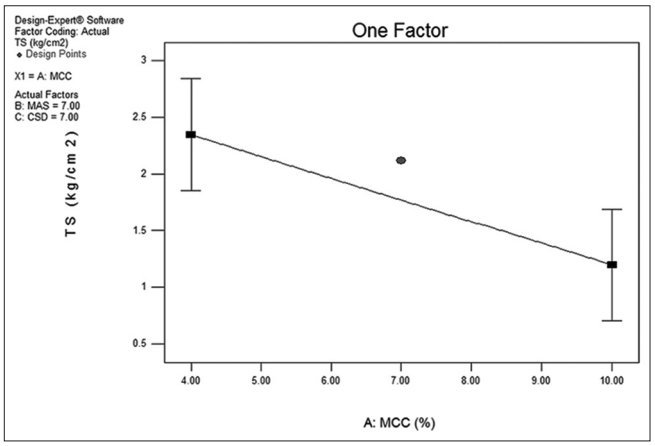


Figure 10: One-factor graphs showing effect of colloidal silicon dioxide on folding endurance

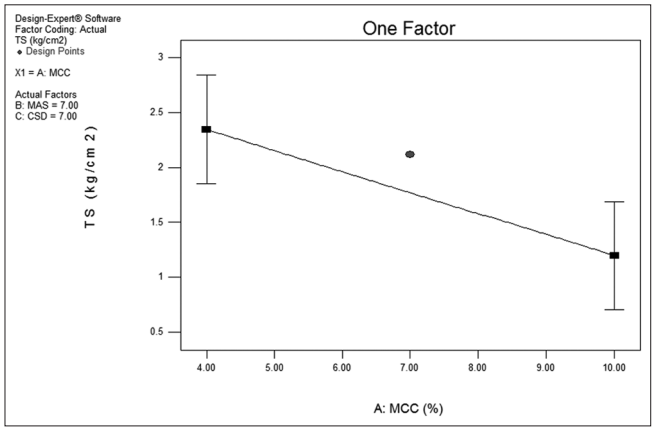


Figure 11: One-factor graphs showing effect of microcrystalline cellulose on tensile strength

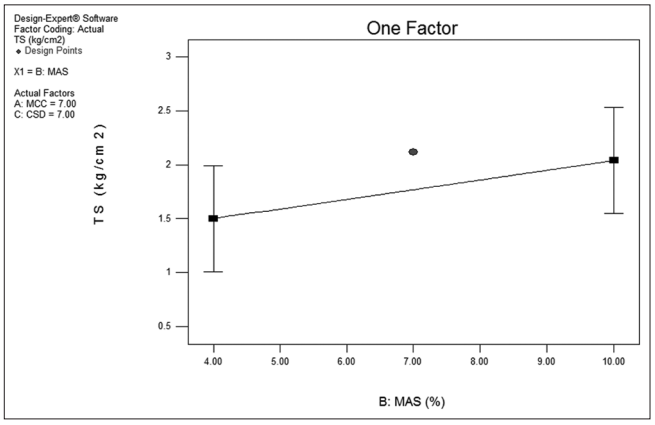


Figure 12: One-factor graphs showing effect of magnesium aluminum silicate on tensile strength

studies as per International Conference on Harmonization guidelines.

Effects of variables

Three independent variables were selected to study their effect on the properties of film. The three variables were concentration of MAS, MCC and CSD. These three variables were studied at two levels thus, a 2^3 full factorial design was applied and eight formulations were developed and evaluated. A centre point batch was included to check statistical control. The effect of these variables on the film properties like disintegration time (DT), tensile strength (TS), folding endurance (FE), PMA, surface

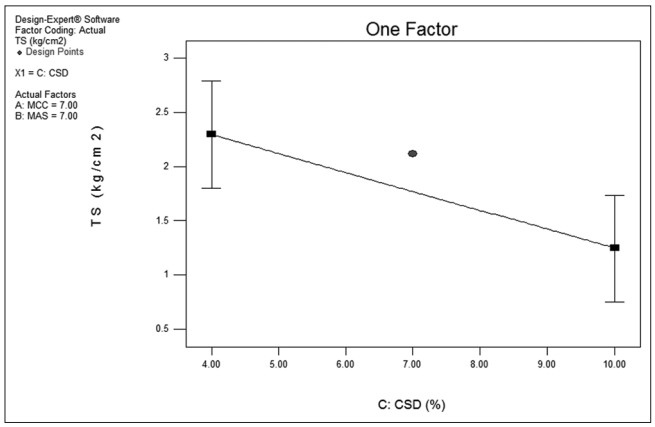


Figure 13 : One-factor graphs showing effect of colloidal silicon dioxide on tensile strength

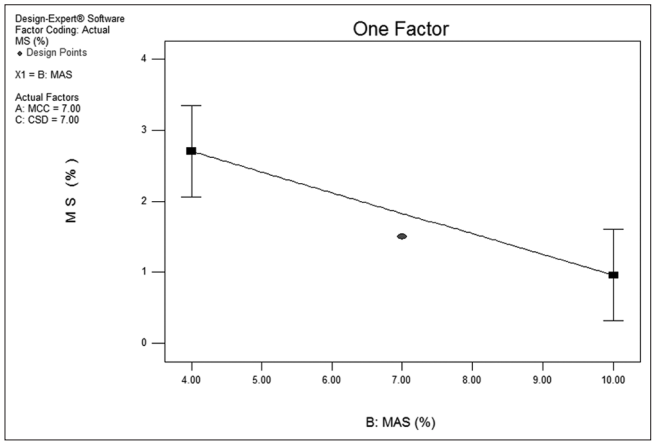


Figure 15: One-factor graphs showing effect of magnesium aluminum silicate on percentage moisture absorption

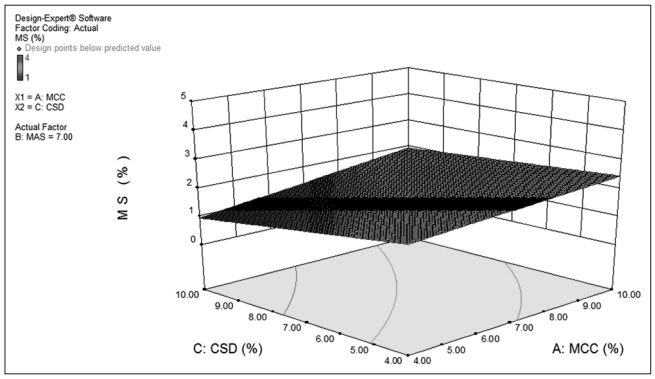


Figure 17: Surface response plot showing the effect of colloidal silicon dioxide and microcrystalline cellulose on magnesium stearate of HD ODS

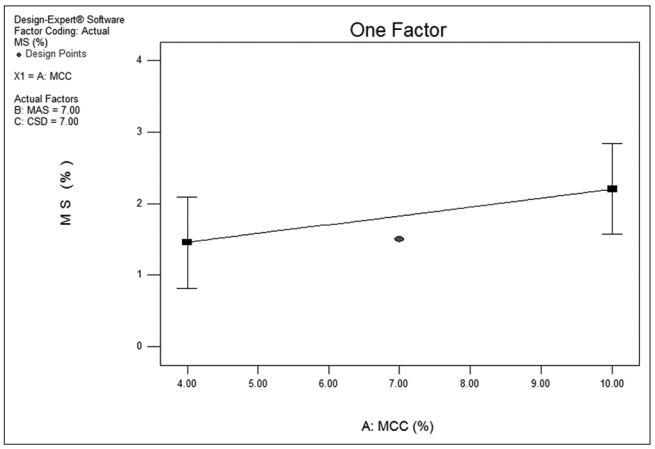


Figure 14: One-factor graphs showing effect of microcrystalline cellulose on percentage moisture absorption

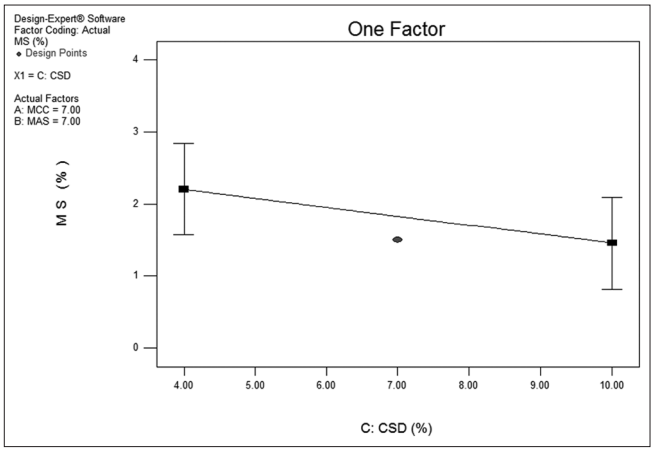


Figure 16: One-factor graphs showing effect of colloidal silicon dioxide on percentage moisture absorption

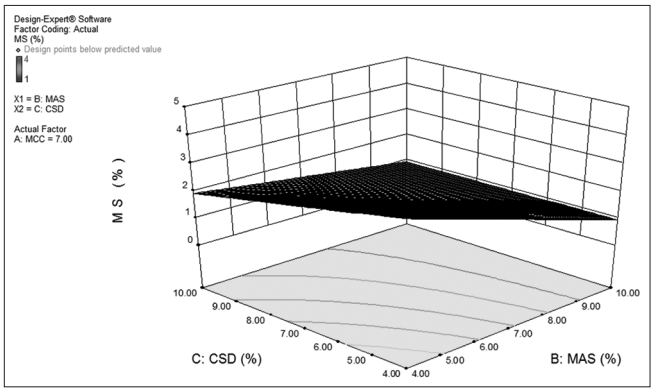


Figure 18: Surface response plot showing the effect of magnesium aluminum silicate and colloidal silicon dioxide on magnesium stearate of HD ODS

morphology, *in vitro* disintegration and dissolution was studied.

Evaluation of films

Folding endurance

The FE along with TS of a film is related to the flexibility of a film and hence represents its physical stability during manufacturing, packing and use. It was measured manually by firmly folding a film repeatedly through the middle. The number of folds on the same crease, required to produce crack in the film was noted as the value of FE.[6,7]

Tensile strength

Tensile strength is maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by cross-sectional area of strip as given in the film equation below:[8]

$$TS = \frac{\text{Load failure} \times 100}{\text{Strip thickness} \times \text{Strip width}}$$

The average of TS of three films was taken as final reading.

Percentage moisture absorption

The PMA test is carried out to check the physical stability of films at high humidity conditions. In the present study, PMA of the films were determined by keeping the preweighed films in desiccator at room temperature for 72 h. Then they were taken out and exposed to 84% relative humidity (saturated solution of potassium chloride). Values for the percentage of moisture uptake, calculated as the percentage of difference between the final and initial weight with respect to the final weight as per the following formula.[9]

$$PMA = \frac{\text{Initial weight - Final weight} \times 100}{\text{Final weight}}$$

Surface morphology determination

For this study a small section of each OTF was cut and then mounted onto stubs using double sided adhesive tape. Then the sections were examined under scanning electron microscope (Phenom desktop SEM) for surface morphology.

Table 1: Formulation of phenylephrine OTF at three loading concentrations (batch size: 1000 films)

Ingredients	Loading of phenylephrine HCl (%)		
	HD	MD	LD
Phenylephrine HCl	29.63	17.40	10.00
HPMC 15 cps	55.55	65.21	75.00
Xanthan gum	3.70	4.34	5.00
Sucralose	11.40	1.65	1.90
Bronopol	0.01	0.01	0.01
PG	6.14	7.21	8.29
Citric acid+lemon flavour	3.56	4.17	4.80

PG: Propylene glycol, HD: High dose, MD: Medium dose, LD: Low dose, HPMC: Hydroxypropylmethyl cellulose, OTF: Oral thin film

Drug content

Five films from each formulation batch were picked randomly and were weighed individually. Each film was agitated in methanol for 24 h and the mixture was suitably diluted to measure absorbance spectrophotometrically at 240 nm. The average drug content was calculated.

Disintegration test

Disintegration time was performed in the USP disintegration apparatus. Simulated salivary fluid (pH 6.8) was used as the medium. The films were placed in the tubes of the container

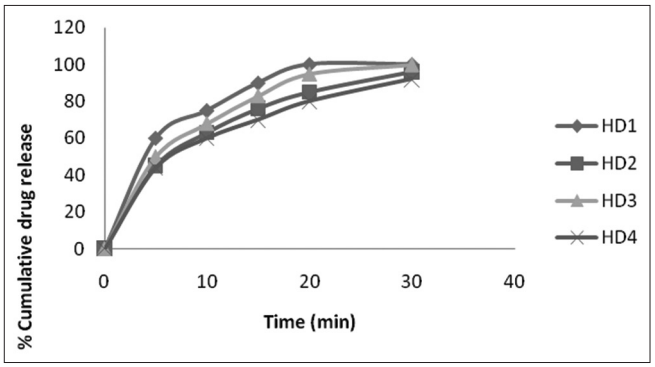


Figure 19: *In vitro* release of phenylephrine HCl oral thin film HD1 to HD4

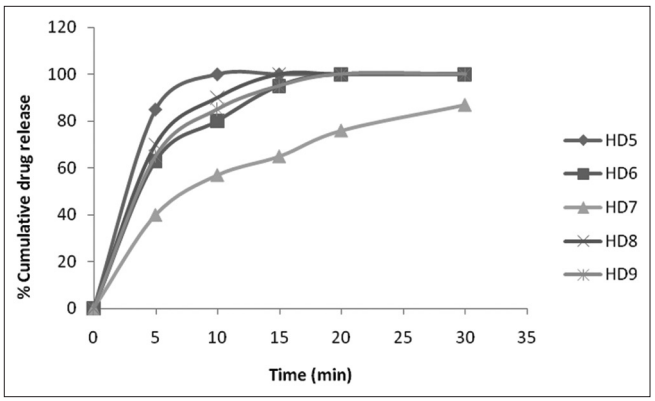


Figure 20: *In vitro* release of phenylephrine HCl oral thin film HD1 to HD4

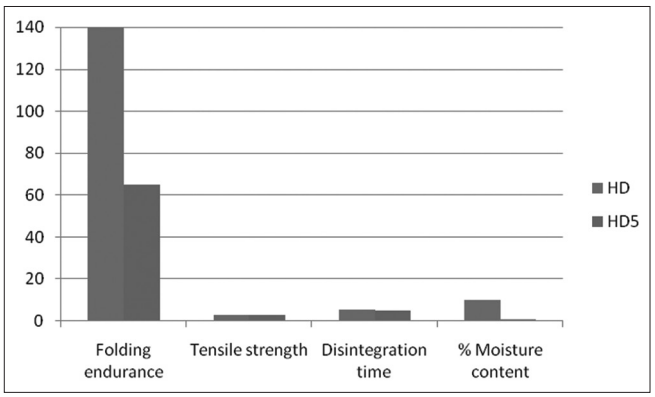


Figure 21: Comparative parameters of initial and optimized formulation

and the disks were placed over it. The average DT of six films from each formulation batch was noted.[10]

In vitro dissolution studies

In vitro dissolution studies were carried out using USP basket type apparatus. Simulated salivary fluid (pH 6.8, 500 ml) was used as dissolution medium at 50 rpm speed (Nishimura *et al*., 2009). At periodic time interval 5 ml sample was withdrawn and replaced with the equal quantity of fresh dissolution medium. Samples were filtered through 0.45-µm Whatman filter paper, and analyzed spectrophotometrically at 240 nm. The *in vitro* dissolution testing studies were performed in triplicate for all the batches.

Stability studies

Stability studies for 6 months were carried out for all the batches at 40 ± 2°C and 75 ± 5% relative humidity, 30 ± 2°C and 75 ± 5% relative humidity. After every month the films were evaluated for the physical appearance, FE, DT, and drug content.

RESULTS AND DISCUSSION

All the phenylephrine HCl OTF's were prepared with three loading concentrations and were evaluated for organoleptic studies along with physical and chemical properties. Results of physical properties and chemical properties as given in Tables 2 and 3 respectively. All the formulations were acceptable with respect to organoleptic characteristics and appearance. It was observed that as the amount of water soluble drug increased in the formulation there was increase in the moisture absorption and resulted films became difficult to separate from surface and became tacky. *In vitro* DT was increased with decreased amount of drug [Figure 1]. Low dose (LD) formulation gave highest disintegration 20.43 s and high dose (HD) formulation gave shortest DT of 5.52 s. Changes in FE and TS of formulations due to different drug loading are shown in Figures 2 and 3 respectively. The study of PMA gives an idea about the stability of film. Because more the moisture absorption properties less stable the final formulations will be. PMA of all the formulations was increased with increased amount of drug [Figure 4]. As drug is hydrophilic in nature, this behavior was expected. Formulation medium dose and LD gave acceptable results with all the selected parameters. Formulation HD showed higher tackiness and tacky films are not acceptable for packing as they tend to reduce patient compliance and convenience because of the difficulty of removal from the surface and also because these films sticks to the hand. Higher moisture absorption during storage may cause microbial growth and degradation of the product. Thus, there was a need to make stabilized tack free film formulations with higher water soluble drug loading capacities.

Microcrystalline cellulose, MAS and CSD are the known good anti-tacking agents. Hence an attempt was made to study these three agents at two levels by using 2^3 full factorial design and one center point batch. Table 4 gives the details of independent variables and their levels chosen for the optimization of phenylephrine HCl OTF. Full factorial design layout on formulation parameters for phenylephrine HCl OTF is given in Table 5. Results of full factorial design are given in Table 6 and response parameters for all these formulations are given in Table 7.

Disintegration time (Y1), FE (Y2), TS (Y3) and PMA (Y4) were selected as response parameters for studying the effect of selected independent variables. Values of "$P > F$" <0.0500 indicate that model terms are significant and values > 0.1000 indicate that the model terms are not significant.

It was observed from Table 7, that model terms were significant for the response Y1, Y2 and Y3 as *P* values were 0.0001, 0.0016 and 0.0435 respectively, while it was nonsignificant for the response Y4 with *P* value 0.0516. Disintegration respone was influenced by all the three factors. Factor A, B and C were significant model term with *P* value 0.0385, 0.0056 and 0.0001 respectively. Factor A and C increased the DT of film as C-values were positive that is, + 0.375 and + 1.958 respectively, wheras factor B showed negative response as C-value was −0.625. All factors A, B and C were negatively affecting the response FE (Y2) with *P* value 0.018, 0.0142 and 0.0025 corresponding to C-value −2.583, −1.583 and −2.417 respectively. Similarly TS (Y3) of the formulation was negatively affected by factor A and C with *P* values of 0.0333 and 0.0449 corresponding to C-value of −0.192 and −0.175 respectively, wheras factor B was insignificant. Factor B showed negative influence on PMA as C-value was −0.292 with *P* value 0.0189. Factors A and C was nonsignificant as $P > 0.0500$.

One factor graph for measured responses were formed to study the effct of independent variables. Three-dimentional plots for the measured response were also formed, based on the model polynomial functions to aceess the change

Table 2: Effect of three loading concentrations on organoleptic and physical properties

Formulation code	Organoleptic characters	Appearance	Tack test	Separation from the surface	Folding endurance	Tensile strength (N/mm^2)
HD	Acceptable	Acceptable	Tacky	Separable with difficulty	140±0.01	3.1±0.12
MD	Acceptable	Acceptable	Tack free	Easily separable	143±0.03	3.5±0.027
LD	Acceptable	Acceptable	Tack free	Easily separable	142±0.02	4.0±0.21

HD: High dose, MD: Medium dose, LD: Low dose

Table 3: Effect of three loading concentrations on chemical properties

Formulation code	DT (s)	Moisture absorption (%)	Drug content (%)
HD	5.52±0.31	10±0.02	98.00±0.56
MD	15.00±0.45	6±0.04	100.00±0.22
LD	20.43±0.10	4±0.03	99.19±0.18

HD: High dose, MD: Medium dose, LD: Low dose, DT: Disintegration time

Table 4: Variables and their levels chosen for the optimization of OTFs

Variables levels	Low	High
A: MCC	4	10
B: MAS	4	10
C: CSD	4	10

OTFs: Oral thin films, MCC: Microcrystalline cellulose, MAS: Magnesium aluminum silicate, CSD: Colloidal silicon dioxide

Table 5: Full factorial design (3^2) layout on formulation parameters for high loading concentration of phenylephrine HCl OTF

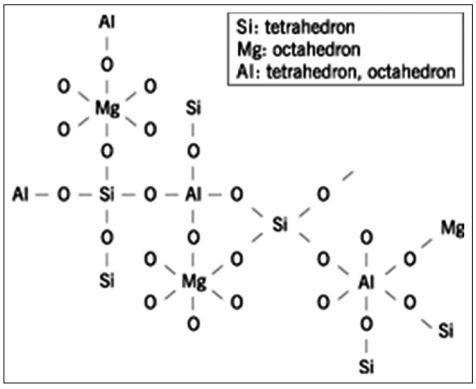
Formulation code	Variable		
	A	B	C
HD1	7.00	7.00	7.00
HD2	10.00	10.00	10.00
HD3	4.00	10.00	10.00
HD4	4.00	4.00	10.00
HD5	4.00	10.00	4.00
HD6	10.00	4.00	4.00
HD7	10.00	4.00	10.00
HD8	10.00	10.00	4.00
HD9	4.00	4.00	4.00

HD: High dose, OTF: Oral thin film

of the response surface. Also the relationship between the dependant and independent variables can be further understood by these plots.

As percentage of MAS increased, DT decreased [Figure 6]. At 10% concentration of MAS DT was 20.05 s while at 4% it was 8.27 s. When effect of MCC was studied, it was observed that increase in amonut of MCC, resulted in incraese in DT to some extent. At 4% of MCC, DT was 12.49 s and at 10% it was 15.21 s. This may be because of cellulosic nature of MCC as it get swelled, [Figure 5] in presence of disintegration media and increases DT. From Figure 7, it was observed that increase in DT was found with incrased level of CSD. As CSD is composed of fumed silica which is highly hydrophobic in nature. It reduces wettability of disintegrating media from the surface of the film and increased the DT.

Folding endurance was decreased with increasing amount of MCC in formulation [Figure 8]. At low level of MCC FE was 65.82 and at highter level it was 50.82. FE was decrased due to insoluble and crystalline nature of microcystalline cellulose which impart less flexibility folding endurance was found to decrease with increase level of factor B as shown in Figure 9. Similarly, at higher percentage of factor B (MAS), FE was 62.5 and at lower percentage it was 53.00. Decrease in FE was comparatively less as compared to factor A and factor C. MAS is composed of three-lattice layers, the different layers can be separated upon hydration, and MAS can exhibit negative charges in the surface layer (-SiO − groups). For this reason MAS may interact with positively charged drugs, such as protonated Phenylephrine HCl. Furthermore, the negative charges of silicate layers of MAS may also interact with positively charged cellulose films that possess improved mechanical properties.[11]



Factor C at low and high level gave FE of 50.98 and 65 respectively [Figure 10]. The reason may be that the presence of anti-tacking agent might be interfering in the inter linking of HPMC and PVA molecules and hence structure flexibility of the films is not achieved.

From Figures 11 and 12 it was revealed that TS of formulation was decreased with increased level of factor A and C respectively, whereas increase in level of factor B increases the TS to desirable extent [Figure 13]. At low level of B (MAS) TS was 1.5 kg/cm^2 and at high level it was 2.02 kg/cm^2. These results suggest that MAS increases the TS and flexibility of formulation.

At 10% and 4% of MCC moisture absorption was 2.22% and 1.45% respectively [Figure 14]. MCC is hygroscopic in nature due to its porous structure. As the amount of MCC is increased in formulation, it adsorbs more moisture from atmosphere and retains it in its cellulosic matrix. From the Figure 15, at 4% of MAS, moisture absorption was 2.69% and at 10% it was 0.94%. Decrease in PMA may be due to either complex three dimensional structure of MAS which provides hydrophobic properties to the film. Presence of CSD in formulation resulted in lowering of the PMA, Figure 16. At low level and high level PMA was 2.16% and 1.45%. Due to submicroscopic (extremely high surface area) and hydrophobic surface, CSD greatly minimized hygroscopicity of the film.

It was observed from Figure 17 that increased in concentration of CSD alone resulted in decreasing PMA. At 4% level

Table 6: Results of full factorial design for high loading concentration of phenylephrine HCl OTF

Formulation code	Separation from the surface	Appearance of film	Tack test	DT (s)	FE	TS	PMA
HD1	Separate	Slightly rough	Tack free	12	60	2.12	1.5
HD2	Separate	Slightly rough	Tack free	20	35	0.50	1
HD3	Separate	Slightly rough	Tack free	17	57	2.50	1
HD4	Separate	Slightly rough	Tack free	21	60	1.02	1
HD5	Separate	Slightly rough	Tack free	5	65	2.70	1
HD6	Separate	Slightly rough	Tack free	11	60	1.07	4
HD7	Separate	Slightly rough	Tack free	23	50	0.80	3
HD8	Separate	Slightly rough	Tack free	8	55	2.30	1
HD9	Separate	Slightly rough	Tack free	10	80	3.00	3

DT: Disintegration time, FE: Folding endurance, HD: High dose, TS: Tensile strength, PMA: Percentage moisture absorption, OTF: Oral thin film

Table 7: Response parameters for high loading concentration OTF

Source	Y1 (DT)		Y2 (FE)		Y3 (TS)		Y4 (PMA)	
	C	*P*	*C*	*P*	*C*	*P*	*C*	*P*
Model	+2.153	0.0001	104.083	0.0016	3.710	0.0439	3.875	0.0516
A	+0.375	0.0385	−2.583	0.0018	−0.192	0.0333	0.125	0.2031
B	−0.625	0.0056	−1.583	0.0142	+0.090	0.2298	−0.292	0.0189
C	+1.958	0.0001	−2.417	0.0025	−0.175	0.0449	−0.125	0.2031

A-MCC, B-MAS, C-CSD. MCC: Microcrystalline cellulose, MAS: Magnesium aluminum silicate, CSD: Colloidal silicon dioxide, DT: Disintegration time, FE: Folding endurance, TS: Tensile strength, PMA: Percentage moisture absorption, OTF: Oral thin film

Table 8: Stability studies data of HD

Months	Physical appearance	Tack test	DT (s)		Drug content	
			40±2°C,75±5% RH	30±2°C, 75±5% RH	40±2°C, 75±5% RH	30±2°C, 75±5% RH
1	Slightly rough	Tack free	5.0±0.67	5.0±0.96	99.12±1.67	99.39±1.91
3	Slightly rough	Tack free	5.1±0.35	5.12±0.67	98.12±1.29	98.78±1.37
6	Slightly rough	Tack free	5.2±0.28	5.14±0.16	98.02±0.92	98.64±0.99

RH: Relative humidity, DT: Disintegration time, HD: High dose

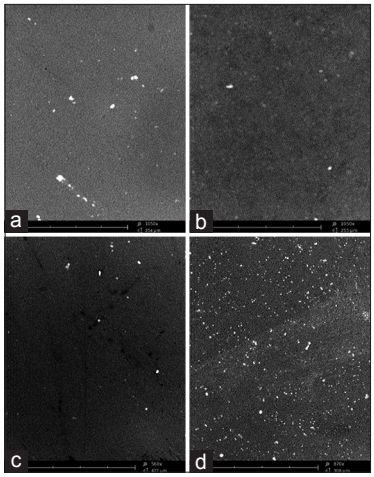


Figure 22: (a) Scanning electron micrographs of PH oral thin film. (a) LD, (b) MD, (c), LD, (d) optimized formula

moisture absorption was 1.94% while at 10% level it was 0.99%. In case of MCC, at lower level, moisture absorption was 1.94% and at higher level it was 2.44%. When both these factors were evaluated in combination at 4% of both these factors moisture absorption was 1.94% and at 10% it was 1.95%. Hydrophobic nature of CSD decreased the PMA whereas porous nature of MCC absorbed the moisture from atmosphere. From this it can be concluded that both these factors interacting with each other when studied in combination. Interaction between factor B (MAS) and C (CSD) showed in Figure 18, at 4% of both of these factors, moisture absorption was 3.396% while at 10%, it was 1.96% and 0.99% respectively. The decrease in PMA may be because of hydrophobic nature of both the excipients which does not allow moisture permeation in film.

All these formulations were further evaluated for comparative *in vitro* dissolution. The release rate of all the formulations is given in Figures 19 and 20. *In vitro* dissolution rate was also correlated with *in vitro* DT. A perusal to Figure 18 indicated that the drug release was highter in formulatation HD5, HD8, HD9 and HD6. Almost 100% of drug release was obtained from formulation HD5 in 10 min due to presence of MAS. More than 80% of drug release was obseved in HD8, HD9 and HD6 in 10 min.

The comparative parameters results for initial and optimized formulation [Figure 21] showed that presence of anti-tacking agents in films decrease the FE as well as PMA. The decreased in PMA is the desirable result whereas decrease

in FE was undesirable. But in concern with packaging and converting of this formulation the value of FE is acceptable. DT and TS of the formulation was not found to be affected by selected independent variables Figure 22 shows the scanning electron micrographs of phenylephrine HCl OTF. Formulation A, B and C was found to be smooth without any striations and roughness. After addition of moisture adsorbent, the image was found to be rough and this might be because of hydrophobic nature of anti-tacking agents in the film. Table 8, showed results of stability studies, optimized formulations were found to be stable for 6 months with respect to physical and chemical properties.

CONCLUSION

In this study, an attempt was made to optimize phenylephrine HCl OTF with three loading concentrations; high, medium and low. Film containing high concentration of phenylephrine HCl was found to be tacky with high PMA as compare to medium and low loading concentration. Hence, the objective of the present study was to investigate the effect of anti-tacking agents namely MAS, MCC and CSD by applying 2^3 full factorial design on improving the film properties of high concentration phenylephrine HCl. Formulation containing microcystalline cellulose and CSD at low level and MAS at high level was found to be suitable for film formation with desirable physicochemical properties, faster disintegration and optimum *in vitro* release. The optimized formulation was found to be stable as per the ICH guidelines. Also, it can be concluded that OTF of phenylephrine HCl can be formulated with 30% drug loading.

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