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FORMULATION AND EVALUATION OF ORODISPERSIBLE FILM OF HYDROXYZINE HYDROCHLORIDE

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ABSTRACT

In the present study, an attempt was made to develop orodispersible film of Hydroxyzine Hydrochloride by solvent casting method. Drug-excipients and excipients-excipients incompatibility study was carried out using fourier transform Infrared Spectroscopy (FTIR) which shows that drug-excipient and excipient-excipient were compatible to each other. Orodispersible film of Hydroxyzine Hydrochloride containing hydroxy propyl methyl cellulose E5LV and hydroxy propyl methyl cellulose E15LV were developed by solvent casting method using propylene glycol as a plasticizer and citric acid as a saliva stimulating agent. Batch H_1(hydroxy propyl methyl cellulose E15LV 100 mg, citric acid 20 mg and propylene glycol 20% w/w) showed excellent appearance, transparency,% elongation 1.7±0.30,tensile strength 35±0.49,folding endurance 770±3 and maximum drug entrapment 98.12%. This result revealed that presence of propylene glycol (20% w/w of polymer) was used which gave good physicochemical properties and citric acid (0.2%w/w of polymer) was rapid disintegration of orodispersible film. Stability studies of the optimised batch H_1 showed that there were no significant changes in appearance, elasticity, folding endurance, thickness, drug entrapment, tensile strength and in vitro disintegration time after storage at 40±2ºC and 75±5%RH for a one month. This approach suggested that the orodispersible film of Hydroxyzine Hydrochloride using hydroxy propyl methyl cellulose E15LV, citric acid and propylene glycol gave rapid disintegration of orodispersible film and provide faster onset of action.

KEYWORDS: Orodispersible film, solvent casting method, Hydroxyzine HCl, HPMC E5LV, HPMC E15LV.

INTRODUCTION

Fast drug delivery system[1-3]

At late 1970s Fast dissolving drug delivery systems (FDDS) were first developed as an alternative to tablet, capsule and syrups for pediatrics and geriatric patients who experience difficulties in swallowing traditional oral solid dosage forms. Over the past decades, fast disintegrating tablets have been produce attraction as a choice for alternative to conventional oral dosage form because of better patient compliance. Fast disintegrating tablets are solid dosage forms containing medicinal substances which disintegrate very fast, normally in seconds, when put on the tongue. Formulation of fast disintegrating tablets technologies entered the market in the 1980, have grown steadily in demand, and their product pipeline are rapidly expanding. New fast drug delivery technologies attach to many pharmaceutical and patient requirements, ranging from improve management of life cycle to convenient dosing for pediatric, geriatric and psychiatric patients with dysphasia. For most therapeutic agents used to produce system effects, the oral administration is first choice as a route of administration, because of many advantages and high patient compliance than other routes of administration.

The concept of fast dissolving drug delivery system (FDDDS) emerged with an objective to improve patient's compliance. These dosage forms rapidly disintegrate and/or dissolve to release the active pharmaceutical ingredient as quick as they come in contact with saliva, thus obviating the need for water during administration, an attribute that makes them highly attractive for pediatrics and geriatrics patient. Difficult in swallowing conventional tablet and capsules is common among all age groups, especially in elderly and dysphagic patients.

Ideal characteristics for a suitable drug candidate selection

- The drug should not have unpleasant taste.
- The dose of drug to should be low dose up to 25mg
- The active pharmaceutical ingredient with smaller and moderate molecular weight is preferable.
- The drug should stable and soluble in oral cavity.
- It should be partially unionized at the oral cavity pH.
- It should permeate oral mucosal tissue.

Orodispersible Film (ODF)[2,3]

Recent development in the technology have presented viable dosage alternative from oral route for pediatrics, geriatric, bedridden, nauseous or noncompliant patients. Lately Buccal drug delivery becomes an important route of drug administration. Different bio mucoadhesive dosage forms have been developed, which includes adhesive unit dosage form ,semi solids, patches and more recently the polymeric films for buccal delivery, which known as orodispersible films. An Orodispersible film, is a novel drug delivery system for the oral drug delivery, which was developed the technology of the transdermal patch as base. This drug delivery system consists of a very thin strip, which is placed on the patient's oral mucosal tissue, quickly wet by saliva, rapidly hydrates and adheres at the site of application. Drug delivery system gives thin, non-sticky, low moisture film which is convenient for dosing and labelling. It is provide ease in handling packaging and application. Typical film has thickness 1 to 10mm and its surface area can be 1 to 20 cm^2. It is easy to handle and apply due to its low dry tack. The typical disintegration time, which is defined as the time at which the film begins to break when brought into contact with water, is only 5 to 10 seconds for the film with a thickness of 2 mm. The dissolving time, which is defined as the time at which not less than 80% of the tested film is dissolved in aqueous media, is around 30 seconds for film with a thickness of 2 mm.

Special features of Orodispersible films[3,4]

The film is thin elegant, It is available in various size and shape. Film should be unobstructive and have an excellent mucoadhesion property. It should be fast disintegrating time and provides rapid release of drug. The dose of drug should be convenient. If drug has bitter in taste then taste masking is easy to possible. It also helps in enhance stability of film. During administration water is not needed and improved patient compliance.

Composition of Orodispersible Film (ODF)[4]

Table 1: Composition of ODF

Drug	1-30%
Water soluble polymer	40-50%
Plasticizer	0-20%
Fillers, colours, flavours	0-40%

Some therapeutic category for ODF[5,6]

A large number of drugs can be formulated as Orodispersible films. Innovative products may increase the therapeutic possibilities in the following indications.

- Pediatrics(antitussive, expectorants, antihistamine)
- Geriatrics (antiepileptic, expectorants)
- Gastrointestinal diseases
- Nausea (e.g. due to cytostatic therapy)
- Pain (e.g. Migraine)
- CNS (e.g. antiparkisonism therapy).

Film forming polymers[5]

Water soluble polymers are used as film formers. The water soluble polymers achieve rapid disintegration, good mouth feel and mechanical properties to the films. The disintegration rate of the polymers is decreased by increasing the molecular weight of polymer film bases. The polymer can be used alone or in combination to obtain the desired film properties. As the film forming polymer is the most essential and major component of the Orodispersible film, at least 45%w/w of polymer should generally be present based on the total weight of dry Orodispersible film. Some of the water soluble polymers used as film former Hydroxy Propyl Methyl cellulose (HPMC) E-5 and E-15, Methyl cellulose A-3, A-6 and A- 15, Pullulan, carboxy methyl cellulose (CMC), Poly vinyl pyrolidone (PVP) K-90, Pectin, Gelatine, Sodium alginate and polymerized resin are a novel film former.

Plasticizers[5]

It is a vital ingredient of the Orodispersible film formulation. It helps to improve the flexibility of the film and reduce the brittleness of the film. It is significantly improves the film properties by reducing the glass transition temperature of the polymer. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of film. The mechanical properties such as tensile strength and elongation to the films have also been improved by the addition of plasticizers. By Variation in their concentration may affect these properties. Glycerol, di-butyl phthalate and polyethylene glycol, low molecular weight polyethylene glycol, dimethyl phthalate, diethyl phthalate, citrate derivatives like tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients. It is used in concentration of 0-20% w/w of dry polymer weight.

Saliva stimulating agent[5]

This agent is using for the purpose of increase the rate of production of saliva that would aid

in the faster disintegration of the rapid dissolving film formulations. More saliva production helps in the faster disintegration of the fast dissolving film formulations. Some of these agents are citric acid, tartaric acid, malic acid and ascorbic acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them. These agents are used alone or combination between 2 to 6% w/w of weight of film.

Active pharmaceutical agent[5]

The Orodispersible film technology has the potential for delivery of different various types of active pharmaceutical ingredients. The dosage form has a limitation of dose of the drug, due to difficult to be incorporated in orodispersible film. The dose of drug is 5%w/w to 30%w/w of active pharmaceutical ingredients can be incorporated in orodispersible film. There are many active pharmaceutical ingredients which are potential candidates for orodispersible film technology, it have bitter taste. This makes the formulation unsuitable for pediatric preparations. So the incorporated active pharmaceutical ingredient in the orodispersible film, the taste of drug needs to be masked. The active pharmaceutical agent has must lower the molecular weight and moderate molecular weight.

Manufacturing method for producing Orodispersible Films (ODFs).[6-7]

(A) Casting

1. Solvent
2. Semi-solid

(B) Extrusion

1. Hot-melt Extrusion
2. Solid dispersion Extrusion
3. Freeze Dried
4. Rolling

MATERIALS AND METHODS

Materials

Hydroxyzine HCl was purchased from Aatur Laboratories, Vadodara. HPMC E15LV and Propylene glycol was supplied from Chemdyes Corporation, Vadodara.

Selection of ingredients for preparing ODFs

Selection of ingredients for preparing ODFS was done on the bases of literature review

different water soluble polymers like pectin, gelatine, PVA, HPLC E5LV, HPMC E15LV and plasticizers like PEG 400, PG and glycerin were screened for their films forming ability. Ingredients such as sweetening agent, saliva stimulating agent, flavouring agent, solvent etc were fixed based on literature review.

Method for manufacture of orodispersible film[8]

Solvent Casting method is used in the manufacturing of orodispersible film of Hydroxyzine HCl. Water soluble ingredients (polymers) will be dissolve in water to form homogenous viscous solution.API and other excipients will be dissolve in suitable solvent to form a clear viscous solution. Both the solutions will mix and the resulting solution will be caste as a orodispersible film and allow to dry.

Preformulation Study: FTIR spectra for drug alone and with excipients were taken using a FTIR spectro photometer with KBr pellets for the identification of the drug and excipients and to study drug-excipients compatibility. FTIR spectra of Hydroxyzine HCl with excipients mixture are shown in figure 2 to 3 respectively and FTIR spectra interpretation are shown in table 2.

Analytical Method Development: A standard stock solution of Hydroxyzine HCl was prepared by dissolving accurately weighed 10 mg of Hydroxyzine HCl in distilled water in a 100 ml volumetric flask and the volume was made up to mark 100 ml with Distilled water to obtain a stock solution of 100 µg/ml.

Evaluation of orodispersible film of Hydroxyzine HCl[9-14]

The orodispersible films were evaluated for their physical, mechanical and other properties followed by drug content uniformity and stability studies.

Appearance

The formulated orodispersible film was observed for visual appearance, colour and transparency.

Weight variation

The assessment of weight variation was performed by weighing individually five film of every formulation on a digital balance. The average weights were calculated and the standard deviation from the average weights was measured.

Thickness uniformity

The thickness of orodispersible film is important for the brittleness of orodispersible film. Thickness is depended on the area of the Petri plate to be spread. The thickness of the orodispersible film is measured by micrometer screw gauge. It is measured at the different three locations of the orodispersible film; a mean value of three locations can be used as a orodispersible film thickness.

Surface pH

The surface pH of the orodispersible film was determined in order to investigate the possible side effects due to changes in pH *in-vivo*, since acidic or basic pH may cause irritation in the oral mucosa. The orodispersible film was tested at placed in Petri-dish. It was moistened in 1 ml of distilled water and kept for half an hour. The pH was noted after bringing electrode of the pH meter in contact with the surface of formulation and allowing equilibrating for 1 min.

Folding endurance

It was determined by repeatedly folding one film of size 2 X 2 cm^2 at the same place till it broke or folded up to 300 times without breaking of the film, the number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

Tensile strength

Tensile strength was determined using an apparatus fabricated in laboratory. A film (2 X 2 cm^2) was cut and fixed to assembly. The weight required to break the orodispersible film was noted simultaneously film elongation will measured with the help of pointer mounted on the assembly. Measurements were done in triplicate for each batch. Tensile strength is the ratio of maximum stress applied to a point of the film at which the orodispersible film specimen breaks. It can be computed from applied force at rupture to the cross sectional area of the fractured orodispersible film as a mean of three measurements and described in the equation-

Tensile strength = break force/ a.b $(1+\Delta L/L)$

Where, Break force = Weight required to break the film (gm)

a= width

b= thickness and

L= length of the patch respectively.

ΔL= the elongation of film at break point.

Elongation

One end of the orodispersible film was fixed between the iron screens to give support to the orodispersible film and another end was connected to the paper holder in which hook was inserted. A thread was tied to this hook, passed over the pulley and a small pan attached to the other end to hold the weight. A small pointer was attached to the thread, which travels over scale affixed on the base plate. The elongation was determined by recording the distance travelled by the pointer before break of the orodispersible film on the scale. The elongation was determined using following formula

$$\%E = \frac{D_f - D_0}{D_0} \times 100$$

Where:- % E = Percentage elongation

D_0 = Distance between the tensile grips before the fracture of the film.

D_f = Distance between the tensile grips after the fracture of the film.

Disintegration time

In vitro disintegration time was determined by visually in a glass dish containing 10 ml of phosphate buffer pH 6.8. The disintegration time is the time at which the orodispersible film starts to break or disintegrates.

Drug content

The orodispersible film unit of the dimensions 2 x 2 cm^2 was placed in 100 ml of pH 6.8 phosphate buffer solution. The solution was diluted by suitable dilutions and was analyzed using UV-spectrophotometer at 232 nm.

Stability study

The orodispersible film of optimized batch was wrapped in aluminium foil and placed in poly bags. Then it was kept in stability chamber at 40±2°C and 75±5% RH and 30±2º and 65±5% RH for duration of one month. The orodispersible films were evaluated for the weight variation, thickness, disintegration time, tensile strength, % elongation and drug content at interval of 15 days.

RESULTS

FTIR spectra for drug alone and with excipients were taken using a FTIR spectrophotometer with KBr pellets for the identification of the drug and excipients and to study drug-excipients compatibility. FTIR spectra of povidone-iodine and povidone-iodine with powder mixture are

shown in figure 1 and 2 respectively. The spectral elucidations for drug alone and powder mixture are shown in table 2.

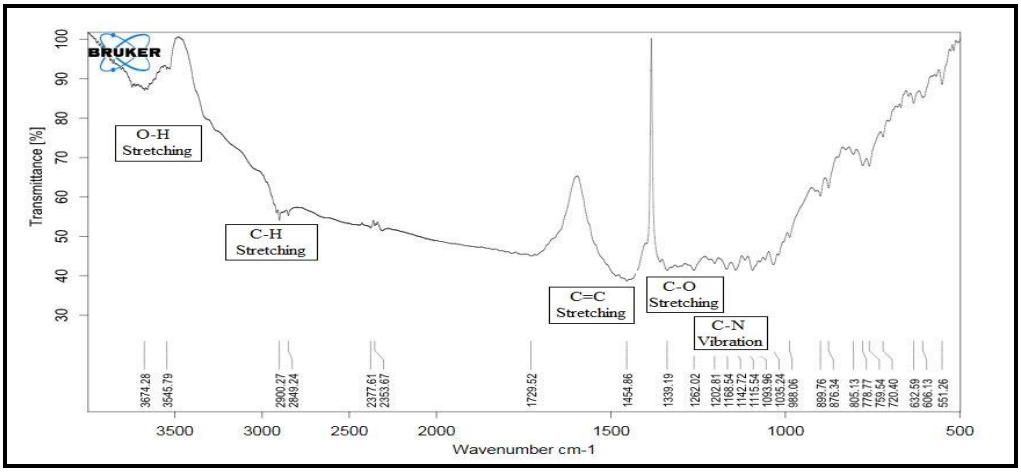

Figure 1: FTIR Spectra of Hydroxyzine HCl

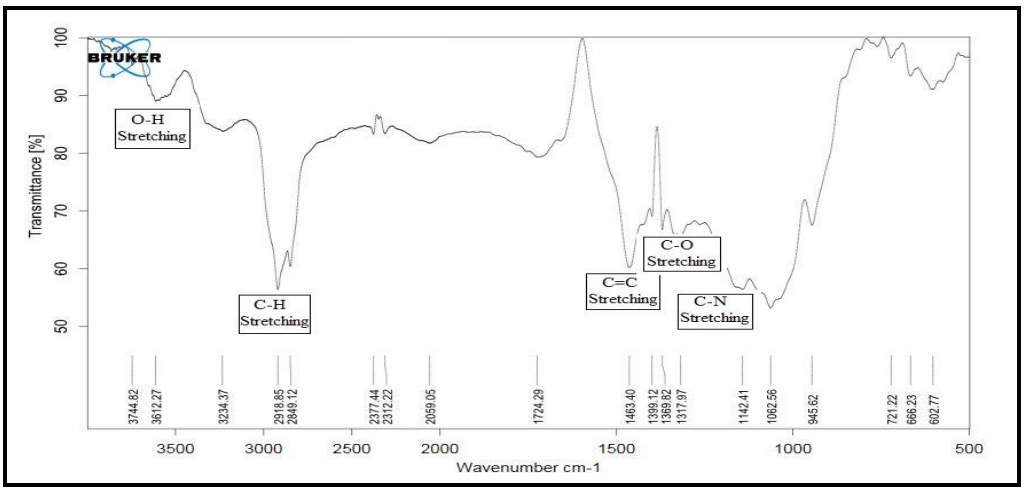

Figure 2: FTIR Spectra of Drug and excipient

Table 2: FTIR spectra Interpretation

	Principle Peaks (cm^{-1})				
Functional group	O-H	C-H	C=C	C=O	C-N
Hydroxyzine HCl	3545.79 cm^{-1}	2900.27 cm^{-1}	1454.86 cm^{-1}	1339.19 cm^{-1}	1168.54 cm^{-1}
Hydroxyzine HCl + excipient	3612.27 cm^{-1}	2918.85 cm^{-1}	1463.40 cm^{-1}	1339.19 cm^{-1}	1142.41 cm^{-1}

Discussion: These results revealed that the drug was compatible with excipients and neither drug decomposition nor drug-excipients interactions were occurred in prepared orodispersible film.

Calibration curve

Calibration curve of Hydroxyzine HCl: Regression co-efficient (R^2) for the drug in water was found to be 0.998 and in the linearity range which showed linear relationship between absorbance and concentration. This standard concentration method obeys beer's law and found to be suitable for the determination of the drug entrapment.

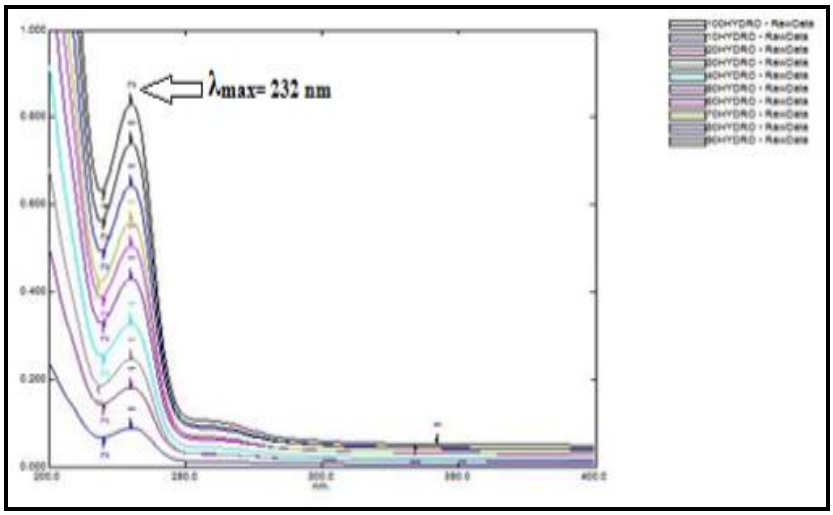

Figure 3: λ_{max} of Hydroxyzine HCl in distilled water

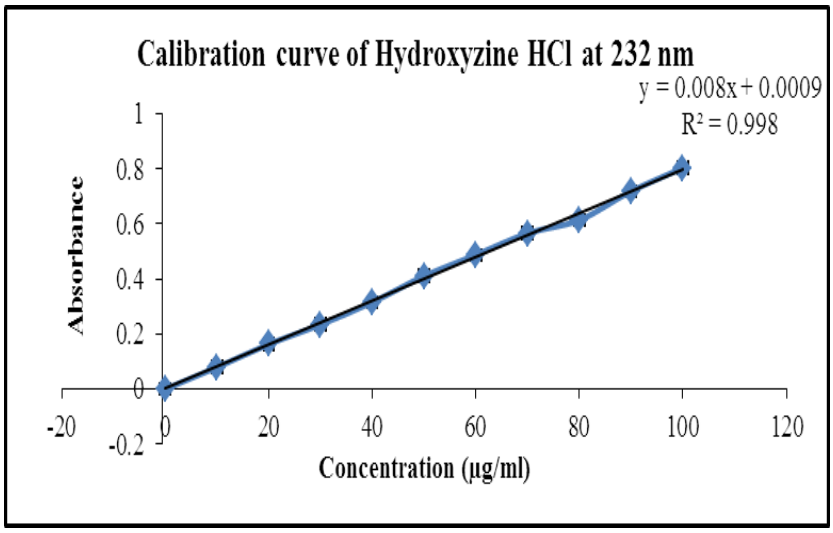

Figure 4: Calibration curve of Hydroxyzine HCl

Formulation optimization of orodispersible film of hydroxyzine HCl using 3^2 factorial design

It is desirable to develop acceptable pharmaceutical formulation in shortest possible time using minimum number of man hours and raw material. Traditionally pharmaceutical formulations after developed by changing one variable at a time approach. This method was

time consuming and it may be difficult to develop an ideal formulation using this classical technique since the joints effect of independent variables are not considered. It was therefore essential to understand the complexity of pharmaceutical formulation using established statistical tools such as factorial design in addition to art of formulation; this technique was effective method of indicating the relative significance of a number of variables and their interactions.

Table 3: Evaluation of orodispersible film batches H1-H9

Batch code	Weight variation (mg)	Thickness (mm)	Surface pH	Folding Endurance	Disintegration time (sec)	Tensile strength (g/cm^2)	%Elongation	%Drug Content
H1	19.5±0.02	0.06±0.002	7.01±0.02	779±2	8±0.577	36±0.51	1.8±0.45	98.81
H2	23.1±0.15	0.04±0.001	7.04±0.01	1001±1	9±0.577	29±0.43	2.3±0.56	97.37
H3	24.2±0.09	0.07±0.001	7.07±0.02	1786±2	12±0.577	35±0.35	8.1±0.23	96.77
H4	18.4±0.02	0.07±0.002	7.03±0.01	360±2	8±0.577	43±0.78	1.9±0.54	98.87
H5	21.4±0.06	0.08±0.003	7.04±0.02	570±3	13±0.577	28±0.67	2.5±0.44	98.56
H6	23.7±0.17	0.06±0.004	7.06±0.03	800±2	13±0.577	32±0.56	7.7±0.34	97.75
H7	18.8±0.03	0.07±0.005	7.01±0.02	599±2	13±0.577	34±0.48	1.8±0.12	96.52
H8	21.6±0.09	0.06±0.002	7.03±0.02	800±1	17±0.577	32±0.23	2.4±0.46	98.75
H9	24.2±0.18	0.04±0.002	7.07±0.02	1560±2	17±0.577	27±0.35	7.6±0.30	97.31

Mean ± SD; n=3

Discussion: An optimised batch of ratio of HPMC E15LV and Citric acid for orodispersible film results was shown in table 3. From this results batch H_1 showed weight variation19.0±0.02mg, thickness 0.06±0.002, surface pH 7.01±0.02, folding endurance 779±2, disintegration time 3±0.5, tensile strength 36±0.51, % elongation 1.8±0.48 respectively. So, Batch H_1 was selected for further optimization of orodispersible film.

Statistical Analysis

For final optimization 3^2 full factorial design was employed to study the effect of independent variables X_1 and X_2 on dependent variables (Y_1) disintegration time, (Y_2) thickness and (Y_3) tensile strength. All the batches are prepared according to the design and analysed using the design expert 9.0.1 software. The software itself suggested respective quadratic model and gave model equation for all dependent variables. The batches H_1 to H_4 was gave the significant value of the variables. The results of ANOVA along with response surface and contour plots generated for each response are given in table 4 to 6 and figure 5 to 10.

Analysis of variance of model equations

ANOVA for Disintegration Time

The polynomial equation derived from the coefficients of estimate in term of coded factor is:

Disintegration Time = +2.38+1.33*A+0.67*B-0.25*AB+0.17*A^2+1.17*B^2_____(1)

Table 4: Results of ANOVA for Disintegration time

Source	SS	DF	MS	R^2	Adj R^2	Pred R^2	P Value
Model	68.17	2	34.08	0.5294	0.4352	0.2870	0.0231 Significant
Residual	60.60	10	6.06	-	-	-	-
Cor total	128.77	12	-	-	-	-	-

Discussion: From the ANOVA table we can conclude that R^2 of disintegration time was found to be 0.8463 respectively. This R^2 indicated that all are close to unity response are best fitted in the model.

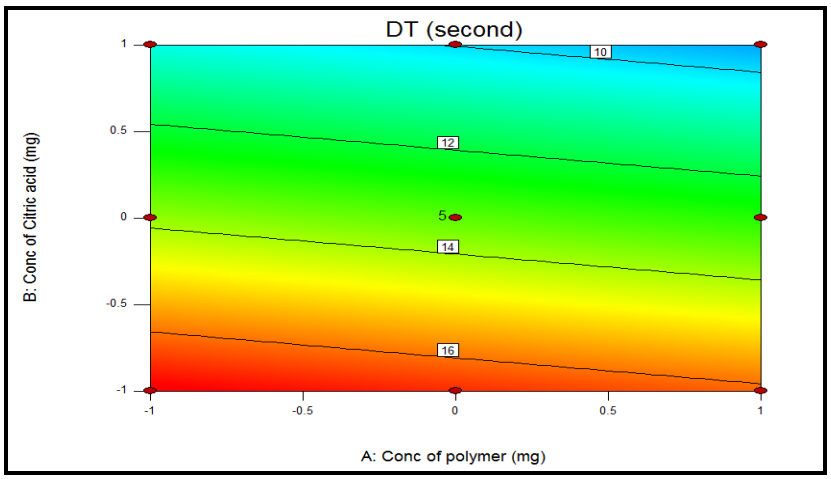

Figure 5: Contour plot for Disintegration Time

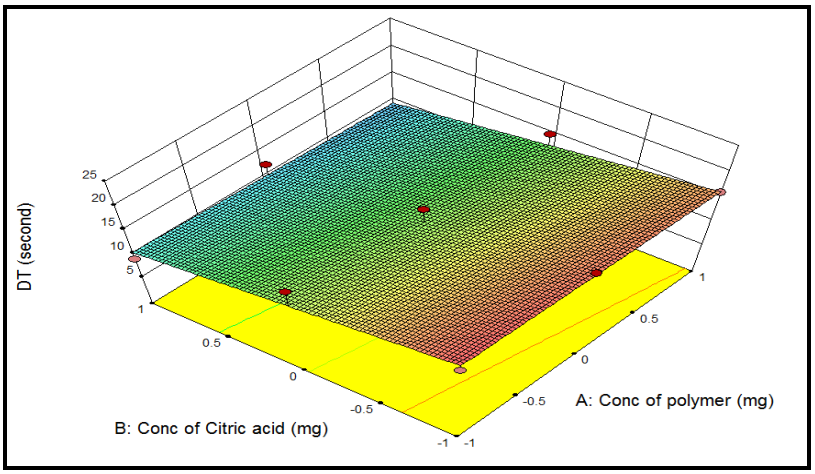

Figure 6: 3D Response Surface for Disintegration Time

Discussion: The figure 5 showed the contour plot of HPMC E15LV and citric acid and figure 6 showed 3D response surface graph of HPMC E15LV and citric acid. This result revealed that minimum concentration of HPMC E15LV and citric acid decrease the disintegration time of the optimized batch H_1.

ANOVA for Thickness

The polynomial equation derived from the coefficients of estimate in term of coded factor is:

Thickness = +0.062+0.015*A-6.020E-018*B _____(2)

Table 5: Results of ANOVA for Thickness

Source	SS	DF	MS	R^2	Adj R^2	Pred R^2	P Value
Model	1.350E-003	2	6.750E-004	0.7737	0.7284	0.5434	0.0006 significant
Residual	3.949E-004	10	3.949E-005	-	-	-	-
Cor total	1.745E-003	12	-	-	-	-	-

Discussion: From the ANOVA table we can conclude that R^2 of thickness was found to be 0.7737 respectively. This R^2 indicated that all are close to unity response are best fitted in the model.

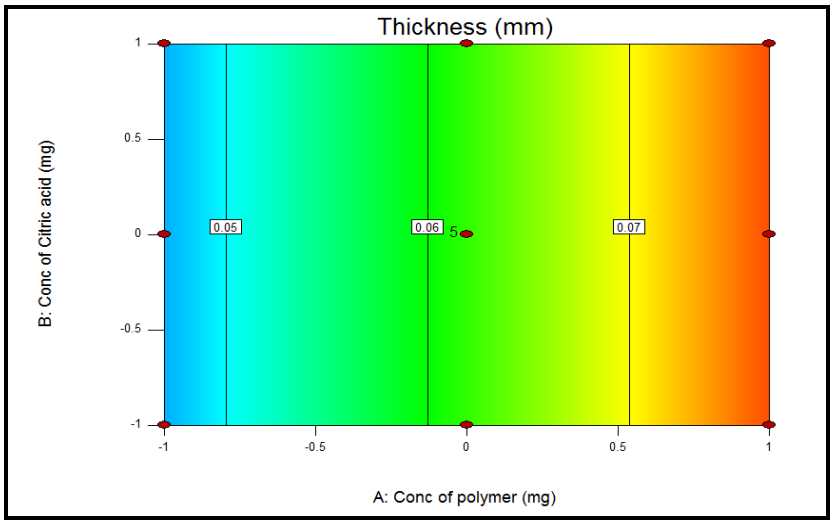

Figure 7: Contour plot for thickness

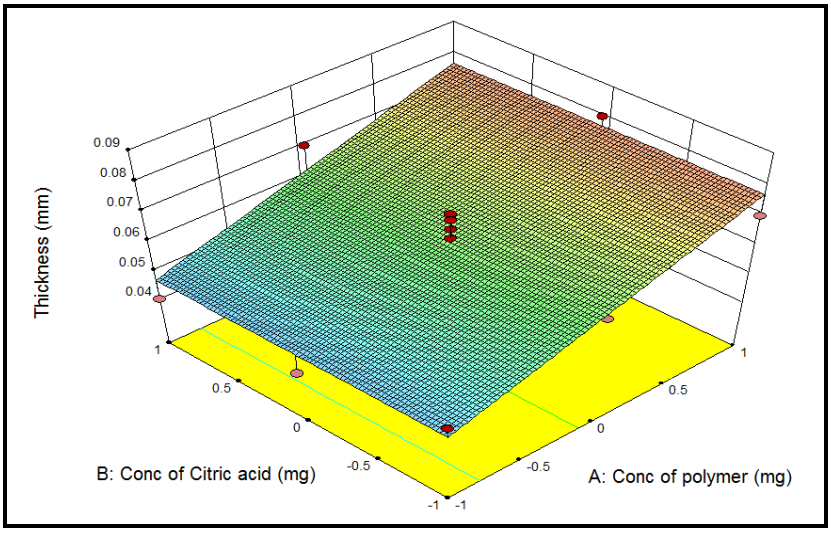

Figure 8: 3D Response surface for thickness

Discussion: The figure 7 showed the contour plot of HPMC E15LV and citric acid and figure 8 showed 3D response surface graph of HPMC E15LV and citric acid. This result revealed that maximum concentration of HPMC E15LV and citric acid increase the thickness of the optimized batch H_1. It is demonstrated that the effect of HPMC E15LV and citric acid on thickness of the film so it decrease the disintegration time of orodispersible film.

ANOVA for Tensile strength

The polynomial equation derived from the coefficients of estimate in term of coded factor is:

Tensile Strength = +34.15+6.83*A+1.17*B _____(3)

Table 6: Results of ANOVA for Tensile Strength

Source	SS	DF	MS	R^2	Adj R^2	Pred R^2	P Value
Model	288.33	2	144.17	0.9557	0.9469	0.9189	<0.0001 significant
Residual	13.36	10	1.34	-	-	-	-
Cor total	301.69	12	-	-	-	-	-

Discussion: From the ANOVA table we can conclude that R^2 of tensile strength was found to be 0.9557 respectively. This R^2 indicated that all are close to unity response are best fitted in the model.

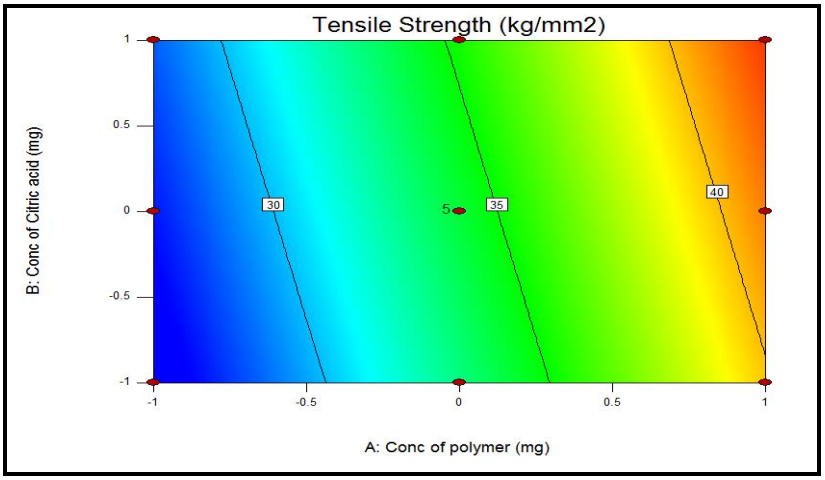

Figure 9: Contour plot for tensile strength

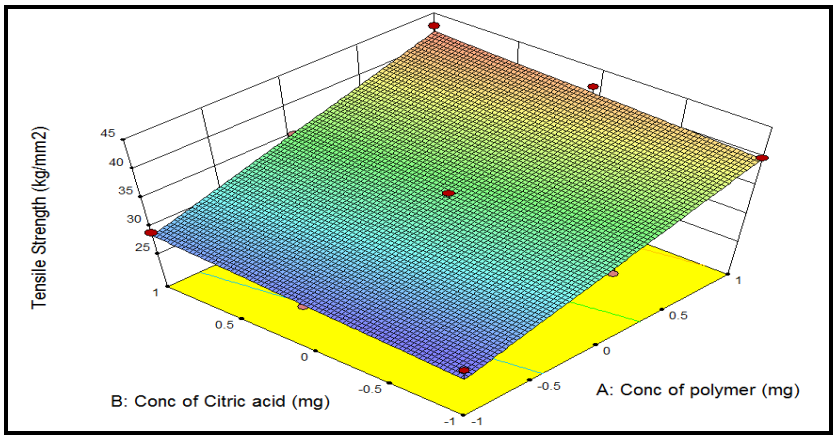

Figure 10: 3D Response surface for tensile strength

Discussion: The figure 9 showed the contour plot of HPMC E15LV and citric acid and figure 10 showed 3D response surface graph of HPMC E15LV and citric acid. This result revealed that maximum concentration of HPMC E15LV and citric acid increase the tensile strength of the optimized batch H_1. It is demonstrated that the effect of HPMC E15LV and citric acid on tensile strength of the film so it decrease the disintegration time of orodispersible film.

Validity of regression equations of 3^2 full factorial design

Comparative table of the observed responses with that of the predicted responses along with t values are listed in table 7

Table 7: Results of Check Point Batch H_1

Batch code	Responses	Predicted value	Experimental value	t_{cal}	t_{tab}
H_1	Disintegration time (Y_1)	9.97655	8±0.5	0.539	2.91
	Thickness (Y_2)	0.0619209	0.06±0.0002		
	Tensile Strength (Y_3)	35.3188	36±0.51		

Discussion: From above results it had been found that t_{cal} and t_{tab} value were found to be 0.539 and 2.91 respectively. Here, t_{cal} value was less than t_{tab} value for all the levels, which suggest that there were no significant different between two results. So equation obtained for selected responses are validated in selected ranges of variables. The close resemblance between the observed and predicted response values assessed the robustness of predictions. These values indicate the validity of generated model.

Results of Stability study

The results revealed that optimized formulation H_1 at 40 ± 2°C temperature and 75 ± 5% RH for one month. Results showed good stability with no remarkable change in disintegration time, thickness, folding endurance and tensile strength up to one month. Observed results indicated that orodispersible film was stable and maintain its mechanical integrity during storage period. Results of stability data are shown in table 8 for the optimized batch (H_1).

Table 8: Results of Stability study

Sr. No	Parameters	Storage Periods (Days) at 40 ± 2 ° C Temperature and 75 ± 5% RH		
		Before storage	After 15 days	After 30 days
1	Disintegration Time	8±0.5	8±0.5	8±0.5
2	Thickness	0.06±0.0002	0.06±0.0002	0.06±0.0002
3	Tensile strength	36±0.51	35±0.68	35±0.49
4	Folding endurance	779±2	775±3	770±3
5	% Elongation	1.8±0.45	1.7±0.23	1.7±0.30
6	Drug content	98.81%	98.25%	98.12%

CONCLUSION

The orodispersible film of Hydroxyzine HCl obtained by solvent casting method showed acceptable mechanical properties like folding endurance, tensile strength, thickness, % elongation and satisfactory disintegration time. The prepared orodispersible film was transparent with smooth surface without having any drug-excipients interactions. The regression analysis of the results leads to equation that describes adequately the influence of the selected variables concentration of hydroxy propyl methyl cellulose E15LV and concentration of citric acid on the responses under study. The higher drug release and permeability and the well observed mechanical properties of film could be helpful for the treatment of allergy with improved patient compliance and provide faster onset of action.

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