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Exploration of Research Opportunities in the Development of Immediate Release Oral Film of Ondansetron Hydrochloride

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Original Research Article

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Abstract: The purpose of present research work was to fabricate patient friendly, immediate release oral film of ondansetron hydrochloride using hydrophilic excipients. The film was prepared by solvent casting method. Hydroxyethyl cellulose, polyvinyl alcohol and polyvinylpyrrolidone k30 along with different plasticizers (peg 400 and pg) were scrutinized for film formulation. The auxiliary excipients used were sodium saccharin and sodium lauryl sulphate. The final selection was done with hydroxyethyl cellulose as a film former and peg 400 as a plasticizer for the film. The drug loaded films of hydroxyethyl cellulose were evaluated for thickness, uniformity in drug content, folding endurance, disintegration time, in-vitro drug release studies, tensile strength and drug-excipient compatibility studies. Taste masking was done by novel sandwich technology (placing the ondansetron hydrochloride film between two listerine pocket pack films). This approach can be used as platform technology for other formulations also. Optimization of film was done by 32 factorial design taking amount of hydroxyethyl cellulose and sodium lauryl sulphate as independent variables, while disintegration time (dt), % cumulative drug release and folding endurance as response variables. Polynomial equations were derived. The validity of equations was checked by preparing check point batches. Response surface plots were constructed using design expert software. This exercise facilitates bio batch selection. Better predictive ability was achieved, when artificial neural network (ann) was used in place of regression analysis. Batch of3 containing hydroxyethyl cellulose showed disintegration time of 16 sec and 94.35 % drug release in 8 minutes.

Keywords: Ondansetron hydrochloride, hydroxyethyl cellulose, solvent casting method, film, convolution, ANN.

INTRODUCTION

There is increase in frequency of cancer chemotherapy induced nausea and vomiting. Hence, there is a need to control such side effects in cancerous patient. The combination of anti-emetics is given, where 20 to 30 % patients are not satisfied, which leads to refractory and anticipatory symptoms [1-3]. However, wide number of patients undertaking therapy complains about the side effects associated with chemotherapy. Amongst them, nausea and vomiting are most common side effects. Nausea and vomiting induced by emetogenic anticancer drugs include acute and delayed events, in which acute emesis occurs within a day of chemotherapy, while delayed event appears after 24 hours and continue for several days.

However, many drugs are associated with serious side effects mainly with dopamine antagonists which leads to extra pyramidal reactions in some patients. Exacerbated research since last many years leads to better understanding of mechanisms of cancer chemotherapy induced nausea and vomiting, which have suggested that 5-hydroxytryptamine (5-HT_3) receptor plays a vital role in this phenomena [4]. Amongst all 5-HT_3 receptor antagonists, ondansetron is prototype of new antiemetic drug developed to control chemotherapy induced emesis. It blocks the depolarizing action of 5-HT as well as emetogenic impulses both at their peripheral region and their central relay [5].

Ondansetron, a 5-HT_3 antagonist is a potent antiemetic drug, which is used in control of nausea, vomiting associated with cancer chemotherapy. It exhibits only 60–70 % of oral bioavailability because of first-pass metabolism [6-9]. The drug has a relative short half-life of 3 to 5 hours. Studies have shown that ondansetron hydrochloride is well absorbed through the buccal route.

Conventional dosage forms such as tablets and orally disintegrating tablets have drawbacks like it is fragile and brittle, also expensive because orally disintegrating tablets are prepared by lyophilization

technique. Fast dissolving film are more preferable for pediatric and geriatric patients (ease of dose administration). It leads to precise and accurate dosing, rapid bioavailability, ease of application (no need of water) and easy to carry.

The fast dissolving oral film would disintegrate and release the drug for dissolution in mouth. Some fraction of the drug may be absorbed from pre-gastric sites such as mouth, pharynx, and esophagus as the saliva passes down into the stomach. In these cases, the bioavailability of drugs from fast dissolving oral film may be greater compared to the conventional oral dosage forms [10]. In view of all the above reasons, an attempt has been made to optimize formulation containing ondansetron as fast mouth dissolving film.

Various water soluble polymers used to formulate fast dissolving films are hydroxypropyl methylcellulose, polyvinyl alcohol (PVA), hydroxyethyl cellulose (HEC), maltodextrin, pullulan, etc. Among all these, lower viscosity grades HEC and PVA tend to produce stronger and flexible films [11]. It is approved by FDA and generally regarded as a tasteless, non-toxic and non-irritant material. Due to low viscosity, it is easily dissolves and gives immediate release of drug. Addition of plasticizer results into adequate mechanical strength of film and thereby increases folding endurance.

Review of literature revealed that combination of synthetic polymers and cellulose derivatives has been patented in the range of 1:7 to 7:1 [12]. In order to prepare non infringing formulation, the use of a single film forming agent along with unique taste masking approach were chosen. The present research work aimed to achieve the objective of taste masking by sandwiching the drug loaded film between two flavored films. This approach can be used as future platform technology.

MATERIAL AND METHODS

Materials

Ondansetron hydrochloride was received as a gift sample from Biocin healthcare, Ahmedabad. Hydroxyethyl cellulose, Polyvinyl alcohol, Polyethylene glycol 400, Propylene glycol, Sodium lauryl sulphate were procured from Astron chemicals, Amedabad. Sodium saccharine was obtained from Yarrow Chem Products, Mumbai.

Table-3.

Evaluation of the fast dissolving film

Thickness

The thickness of each film was measured using a screw micrometer gauge at three locations and the mean thickness was calculated [19].

Folding endurance

Drug-excipient compatibility study

The differential scanning calorimetric analysis (DSC) and Fourier transform infrared spectroscopy (FTIR) were performed to check the compatibility between the components present in the dosage form. DSC was performed using Perkin Elmer DSC-7, Norway, USA, to study the thermal behavior of ondansetron hydrochloride with excipients. The samples (2-4 mg) were heated in hermetically sealed flat-bottomed aluminum pans under nitrogen flow (20 ml/min) at a scanning rate of 100 °C/min from 25 to 200 °C [13]. Empty aluminum pans were used as the reference standard. Ondansetron hydrochloride and hydroxyethyl cellulose were subjected to the FTIR spectroscopy in order to detect the existence of interaction between drug and excipient. The procedure consisted of dispersing a sample (drug alone, excipient alone and mixture of drug and excipient) in KBr to prepare 10 % of mixture. The samples were subsequently compressed in KBr press. The sample was placed in light path and spectrum was recorded at a resolution of 2 cm^{-1} over a frequency range of 4000 to 400 cm^{-1}. KBr was used as blank for entire study.

Preparation of fast dissolving film

Fast dissolving films were prepared using solvent casting technique. Aqueous Solution-I, was prepared by dissolving polymer in 100 ml of water with stirring for 1 hr to remove all the air bubbles and to produce a clear solution. Aqueous Solution-II, was prepared by dissolving pure drug, sweetener, surfactant and plasticizer in distilled water. The aqueous solutions - I and II were mixed and stirred for 1 hr [14]. The solutions were casted into a petri dish with 9 cm diameter and dried in oven at 45-50 °C for 24 hr [15,16]. The films were carefully removed from the petri dish and checked for any imperfection and cut according to size required for testing.

Experimental design

A two factor, three level (3^2) full factorial design was chosen for optimization of formulation. The concentration of hydroxyethyl cellulose (X_1) and concentration of sodium lauryl sulphate (X_2) were selected as independent variables. All the other formulation and process variables were kept constant throughout study. The disintegration time (Y_1), percentage drug release (Y_2) and folding endurance (Y_3) was selected as dependent variables. Design-expert software (v.8.0.7.1, Stat-ease Inc.) was used for the evolving of the mathematical models [17,18]. The design layout and the results are shown in

Folding endurance was determined by repeatedly folding the film at the same place till it break. The numbers of times the film can be folded at the same place without breaking give the value of folding endurance [20].

Disintegrating time

The in-vitro disintegrating time was measured (n=3) for film (1 x 1 cm) of each batch in 10 ml of pH 6.8 phosphate buffer. The time for start to disintegrate of the film was recorded as a disintegrating time. The average of three measurements was taken into consideration [21].

Modified disintegration apparatus

Neither standard time nor pharmacopoeia disintegration test method for orodispersible films (ODFs) exists. The USP disintegration test for tablets and capsules poses significant challenges for end-point determination when used for ODFs. In current study, a newly developed disintegration test unit (DTU) against the USP disintegration test [22]. It holds the ODF in a horizontal position, allowing top-view of the ODF during testing. A gauge study was conducted to assign relative contribution of the total variability from the operator, sample or the experimental set-up. Precision was compared using commercial ODF products in different media. Agreement between the two measurement methods was analyzed.

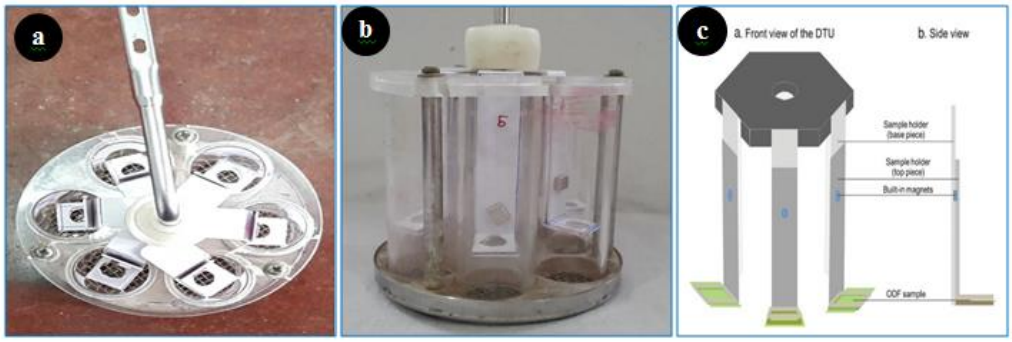

Fig-1: (a) Front view of the DTU with ODFs loaded in the sample holder, (b) side view of a single station sample holder of the DTU, and (c) up-stroke position during the run

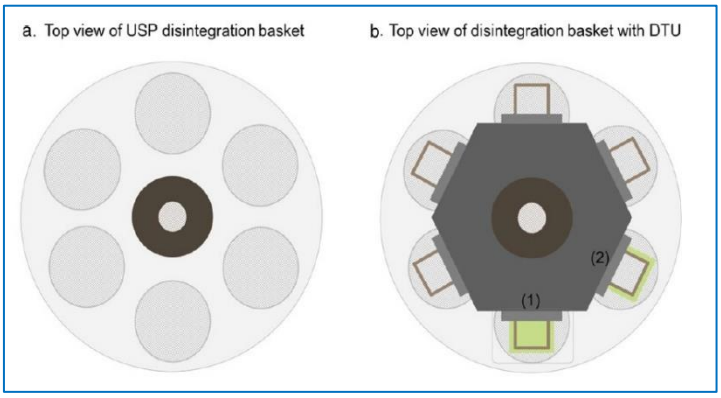

Fig-2: Diagram of the DTU mounted onto the USP disintegration apparatus basket

a) Top view of the USP disintegration basket without the DTU. b) Top view of the USP disintegration basket with the mounted DTU (1) Example of ODF at the start of the disintegration test and (2) Disintegration end-point when the ODF is broken in the viewing are

Removal from petri dish

The ease of film separation from the petri dish was considered as one of criteria for the best film from among prepared (preliminary batches) as well as for the selection of the polymer for further studies [23].

Measurement of mechanical property

The mechanical property of the film given idea about extent of film can withstand the force or stress during processing, packaging, transport and handling. Mechanical properties of film were evaluated using universal testing machine (QTS texture analyzer (Brookfield) software: Texture Pro v2.1) [24]. Film strip with dimension 60 x 20 mm and free from air bubbles or physical imperfections was held between two clamps. During measurement, the strip was pulled at a speed of 30 mm/min. The values of mechanical properties were recorded when the film broken [25]. Results from film samples, which broken at and not between the clamps, were not included in calculations. Measurements were run in triplicate for each film.

Tensile strength

Tensile strength is the maximum stress applied to a point at which the film specimen breaks. The tensile strength (TS) can be calculated by dividing the maximum load by the original cross-sectional area of the specimen and it is expressed in force per unit area (N/mm^2) [26].

Tensile strength (N/mm^2) =	Force at film breaks (N)
	Initial cross-sectional area of the sample (mm^2)

***In-vitro* drug release study**

In the present study a simulated oral cavity model was developed using a set of denture and artificial saliva reservoir. The test was conducted in pH 6.8 phosphate buffer and the basic device was procured from dentist to mimic the area of the oral cavity installed with web camera for online recording provision. Design of simulated oral cavity model apparatus with three components: i) The artificial salivary fluid reservoir, ii) The simulated oral cavity, iii) Fluid flow regulator [27].

The reservoir contains pH 6.8 phosphate buffer; the liquid was transferred through a tube which control flow rate by regulator. Fluid enters into the oral cavity surrounding the artificial tongue. The simulated oral cavity, which is an adult dental set of lower and upper jaw. It was assembled on the tray which is connected with sampling tube. The artificial spongy tongue was placed at the lower jaw. A tube connected with reservoir was supplying fluid to the tongue at controlled rate, which mimicked the secretion rate of saliva. Previously wetted Whattman filter paper was kept on spongy tongue to facilitate base for formulation retention. The flow rate was maintained at 1-3 ml/min. The study was carried out for 10 minutes. At the interval of 2 minute, fluid is collected from bottom and analyzed at 310 nm using UV-Visible Spectrophotometer [28].

Artificial neural network (ANN)

Optimization techniques are abundant in pharmaceutical industry. In general, all the required information should be obtained from as few experiments as possible. Conventional techniques such as response surface models or simplex optimization are often used. With the advent of the computer in the laboratory, a new class of optimization problems arose which could not be tackled with the standard methodologies. For these research type problems, new strategies such as simulated annealing (SA), genetic algorithms (GA) and artificial neural network are applied. Artificial neural network (ANN) is now become more efficient technique for the optimization of pharmaceutical formulation compared to multiple linear regression analysis (MLRA) [29]. In the present investigation multiple linear perception (MLP) tool of ANN was implicated for the optimization of fast dissolving film of ondansetron hydrochloride using 3^2 full factorial design and the results obtained were evaluated using ANN for the optimization purpose. Fast dissolving film was prepared using hydroxyethyl cellulose as low viscosity grade polymer and solvent casting technique as method of preparation. Concentration of hydroxyethyl cellulose (X_1) and concentration of sodium lauryl sulphate (X_2) was selected as independent variable, while disintegration time (Y_1), percentage drug release (Y_2) and folding endurance (Y_3) was selected as dependent variables. Results of disintegration time, percentage drug release and folding endurance obtained by factorial analysis was chosen as set of ANN training. The set of data was trained using MLP tool for ANN training using software Neurosolution v7.0.0. [30]. Data was trained for satisfactory results.

Comparison of optimized film formulation with that of marketed film formulation

Optimized batch of film formulation which was obtained from QbD approach is compared with standard marketed formulation (Vomikind, 8mg) for drug content uniformity, disintegration time and physical appearance.

RESULTS AND DISCUSSION

Drug-excipient compatibility study

The DSC curves of ondansetron hydrochloride, physical mixture of film forming polymer containing ondansetron hydrochloride, is shown in Fig-3. The ondansetron hydrochloride showed exothermic peak at 186.87 °C corresponding to its melting point (176-180 °C). There was a negligible change in the melting exotherm of physical mixture of drug and HEC compared to pure drug. Physical mixtures showed exotherm in the range of which is corresponding to the melting point of pure drug. This result clearly verified that ondansetron hydrochloride with HEC was thermodynamically stable.

The FTIR spectra of ondansetron hydrochloride with excipients are shown in Fig-4.

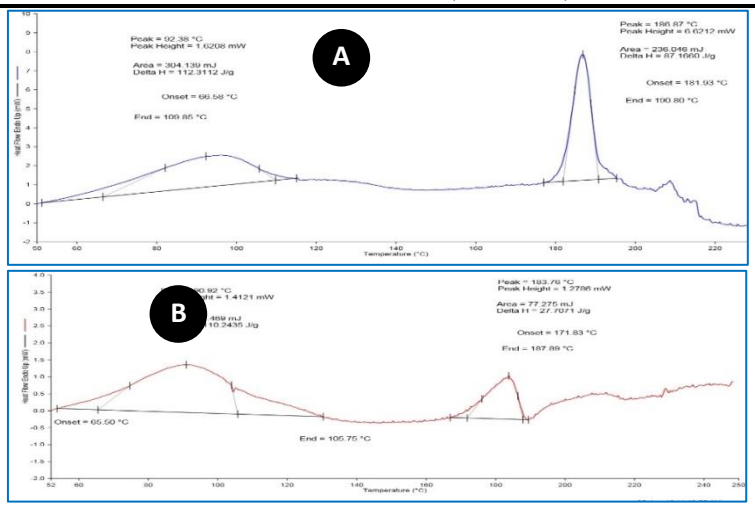

Fig-3: DSC thermogram of (A) Pure drug, and (B) Drug with HEC

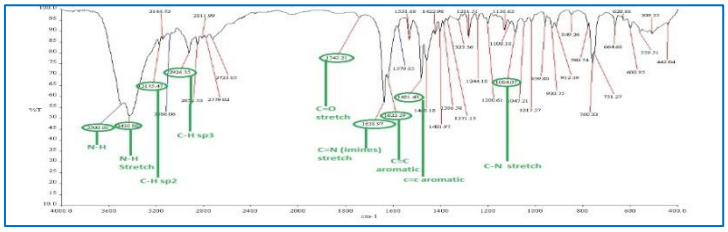

Fig-4: FTIR spectra of ondansetron hydrochloride with excipients

Preparation of fast dissolving film

Result of all preliminary trial batch depicted in Table-1 and Table-2, P1 to P4 (PVP K30), Q1 to Q4 (PVA), R1 to R4 (HEC). The batches P2 to P4 (PVP K30), Q1 to Q4 (PVA), R1 to R4 (HEC) gave an acceptable film except batch P1, which is found like poorly removed from petri dish, because of low concentration of polymer.

Formulation containing PVP K30, PVA, and HEC with PEG 400

The thickness of the film varied from 0.1 to 1.5 mm of all batches. The batch R2 containing 2% HEC showed higher folding endurance. The disintegration test was performed for all batches which showed result in range of 33 to 176 sec. The values indicating that as the concentration of polymer increased, the thickness, DT as well as folding endurance were gradually increased.

Table-1: Evaluation parameters for film prepared from polymers with PEG 400

Batch	PVP K30 (%w/v)	PVA (%w/v)	HEC (%w/v)	PEG 400 (ml)	Thickness[#] (mm)	Folding endurance[#]	DT[#] (sec)	Removal from dish	Physical characteristic
P1	1	-	-	0.1	-	-	-	+	Sticky
P2	2	-	-	0.2	0.43±0.02	65±4	124±4	++	Poor
P3	3	-	-	0.3	0.69±0.08	47±1	171±3	++	Poor
P4	4	-	-	0.4	0.75±0.03	54±3	173±2	++	Poor
Q1	-	1	-	0.1	1.20±0.10	65±3	103±2	++	Sticky
Q2	-	2	-	0.2	0.70±0.17	123±2	72±2	+++	Whitish hazy
Q3	-	3	-	0.3	1.30±0.40	142±2	76±1	+++	Whitish hazy
Q4	-	4	-	0.4	1.40±0.57	154±1	84±2	+++	Whitish hazy
R1	-	-	1	0.1	1.33±0.21	75±3	43±3	+++	Non sticky
R2	-	-	2	0.2	0.16±0.12	166±2	34±2	+++	Non sticky
R3	-	-	3	0.3	0.18±0.42	152±2	53±1	+++	Non sticky
R4	-	-	4	0.4	0.22±0.16	172±1	67±1	+++	Non sticky

[#]mean ± SD (n=3). (Rating: Sticking more: +, Moderate: ++, Good: +++)

The hydroxyethyl cellulose gave a good-quality film with acceptable physical characteristics as well as satisfying disintegrating criteria, while PVA and PVP K30 did not show good result in terms of flexibility, strength and DT as compared to HEC. Also, film prepared with PVA looked whitish hazy, non-clear which would be rejected by patient due to its appearance. From this study, it may be suggested that films formed with 2 to 4 % of polymer HEC showed optimum mechanical strength and disintegration. Hence, PVA and PVP K30 was not selected for further study.

Formulation containing polymer PVP K30, PVA and HEC with PG

Table-2: Evaluation parameters of prepared film of polymers with PG

Batch	PVP K30 (%w/v)	PVA (%w/v)	HEC (%w/v)	PG (ml)	Thickness[#] (mm)	Folding endurance[#]	DT[#] (sec)	Removal from dish	Physical characteristic
P1	1	-	-	0.1	-	-	-	+	sticky
P2	2	-	-	0.2	0.43±0.75	45±1	105±1	++	Non sticky
P3	3	-	-	0.3	0.68±0.23	67±2	157±2	++	Non sticky
P4	4	-	-	0.4	0.80±2.36	58±1	169±1	+++	Non sticky
Q1	-	1	-	0.1	0.70±1.35	69±3	124±1	++	Non sticky
Q2	-	2	-	0.2	0.93±2.36	45±1	143±2	++	Non sticky
Q3	-	3	-	0.3	0.45±2.64	61±1	125±1	+++	Non sticky
Q4	-	4	-	0.4	0.73±0.94	57±1	90±1	+++	Non sticky
R1	-	-	1	0.1	0.30±0.50	107±1	54±1	+++	Non sticky
R2	-	-	2	0.2	0.11±0.21	154±1	36±2	+++	Non sticky
R3	-	-	3	0.3	0.24±1.25	126±1	42±3	+++	Non sticky
R4	-	-	4	0.4	0.29±0.13	137±3	45±1	+++	Non sticky

[#]mean ± SD (n=3). (Rating: Sticking more: +, Moderate: ++, Good: +++)

Influence of plasticizer

The PEG 400 is best plasticizer than propylene glycol for film formulation. Film forming with PEG 400 has better transparency, acceptable physical characteristics, flexibility, folding endurance, less disintegration time, less brittle in nature than propylene glycol. Hence, from the formulation point of view PEG 400 is better than PG; therefore, PEG 400 was selected for further study.

Experimental design

To study all the possible combinations, a two-factors at three-level, full factorial design was constructed and conducted in a fully randomized order. The dependent variables measured were disintegrating time (Y_1), percentage drug release (Y_2) and folding endurance (Y_3). The composition and responses of the 3^2 design are shown in Table-3.

Table-3: Design layout and response value for 3^2 Factorial designs

Independent variables	**Levels**		
	-1 (Low)	**0 (Medium)**	**+1 (High)**
X_1: Amount of HEC (%)	1.7	1.9	2.1
X_2: Amount of SLS (%)	0	0.5	1

Batch	**Independent Variables**		**Response values**		
	X_1	**X_2**	**Y_1**	**Y_2**	**Y_3**
OF1	0	-1	19	86.12	254
OF2	-1	0	22	90.17	223
OF3	0	1	16	94.35	256
OF4	1	0	28	89.69	238
OF5	1	1	32	91.63	237
OF6	0	0	18	90.85	255
OF7	-1	-1	23	83.67	224
OF8	1	-1	34	84.64	236
OF9	-1	1	24	90.66	225

Response variable	Constraints
DT	20-25 sec
% CDR	90-95%
Folding endurance	250-300

Criteria for optimized formulation

The criteria for selection of optimum formula was primarily based on the desired values of the response parameters, i.e. DT, %CDR and folding endurance (see Table-3). The formulation corresponding to optimum responses were prepared and evaluated. Resultant experimental data was quantitatively compared with predicted values and % error was calculated.

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2$$

Where Y is the dependent variable, β_0 is the arithmetic mean response of nine runs, and β_1 is the estimated co-efficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing factor at a time from its low to high values. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non linearity.

The DT (Y_1), % CDR (Y_2) and folding endurance (Y_3) for nine batches (OF1 to OF9) was determined. The fitted equations (full and reduced) relating the responses Y_1, Y_2 & Y_3 to the transformed factor was investigated. The polynomial equations may be used to draw conclusion after considering the magnitude of co-efficient and the mathematical sign it carries (i.e. negative or positive).

Disintegration time (Y_1)

The equations representing the quantitative effect of the formulation variables on disintegration time is shown in Table-4.

Table-4: Regression analysis of DT (Y_1)

R square	0.959
Adjusted R square	0.893
Co-efficient	P value
$\beta_0 = 16.33$	-
$\beta_1 = 4.17$	0.015
$\beta_2 = -0.67$	0.481
$\beta_{12} = -0.75$	0.514
$\beta_1^2 = 9.3$	0.007
$\beta_2^2 = 2$	0.258

Regression coefficients, statistically insignificant ($p > 0.05$)

The full model equation representing the quantitative effect of independent variables on Disintegration time is:

$$DT\ (Y_1) = 16.33 + 4.17X_1 - 0.67\ X_2 + 9.5X_1^2 + 2X_2^2 - 0.75X_1X_2$$

Table-4), it was shown that only effect of X1 is significant. So, polynomial equation has reduced form as shown in following equation. The factor X_2, X_1X_2 interaction and the polynomial term X^2 showed $p>0.05$ and therefore it was omitted from the full model shown above. The reduced or the refined model is shown below:

The value of R^2 was found to be 0.959. Equation gives positive value of only X_1 which indicates X_1 have positive effect on DT. From regression analysis for DT (

$$DT\ (Y_1) = 16.33 + 4.17X_1 + 9.5X_1^2$$

The plot of observed DT versus predicted DT (Fig-5) shows straight line. Therefore, it may be concluded that the equation has good predictive ability.

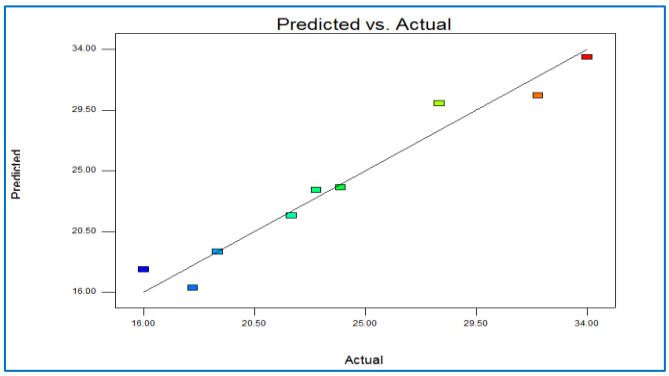

Fig-5: Predicted vs. actual plot (Y_1)

From the viewpoint of QbD, it may be concluded that the factor X_1 (concentration of polymer) is a critical formulation variable for preparing the film with desirable characteristic of disintegration time. Hence, it was concluded that X_1 had positive effect on DT, which indicates that as the polymer concentration increased, DT also increased. The best way to look at the output is to draw 2D contour plot. The contour plot of DT reveal non-linearity (Fig-6).

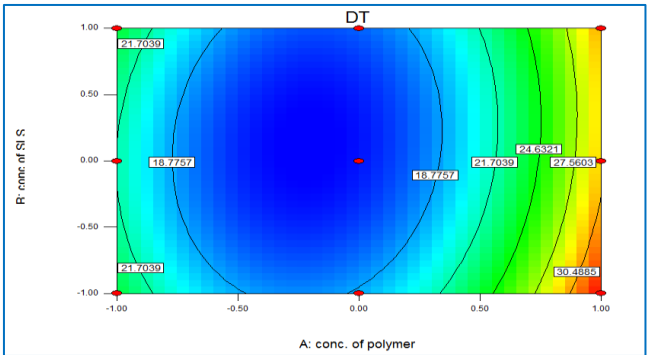

Fig-6: Contour plot for influence of various level of polymers on DT

The Fig-7 shows 3D response surface plot between X_1 and X_2 is non-linear in nature and highest response was seen with high (+1) level of concentration of HEC and low response was seen with low level (-1) of concentration of HEC. It may also be concluded that with change in concentration of HEC significant change on DT was observed, whereas the concentration of SLS causes less influence on DT.

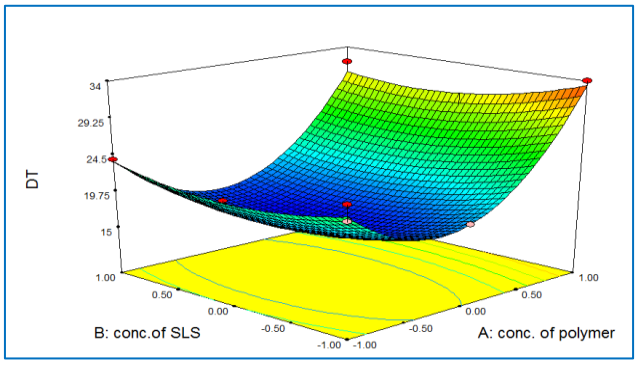

Fig-7: Response surface plots for influence of various level of HEC and SLS on DT

Table-5: Comparison of DT for optimized batch using USP-DT and MDTU-DT

Sample	USP-DT	MDTU-DT
Optimized batch	16±1	11±2
Marketed preparation	19±3	13±1

[#]mean ± SD (n=3). USP-DT: USP disintegration apparatus and MDTU-DT: modified disintegration test unit.

Percentage drug release (Y_2):

The equations representing the quantitative effect of the formulation variables on % CDR is shown in

Table-6.

The full model equation representing the quantitative effect of independent variables on percentage drug release is:

$$\%CDR\ (Y_2) = 91.59 + 0.24X_1 + 3.71X_2 - 2.02X_1^2 - 1.73X_2^2$$

The value of R^2 was found to be 0.97. The factor X_1, X_1X_2 interaction showed $p>0.05$ and therefore it was omitted from the full model shown above. The reduced or the refined model is shown below:

Reduced model equation is as follows:

$$\%CDR\ (Y_2) = 91.59 + 3.71X_2 - 2.02X_1^2 - 1.73X_2^2$$

The plot of observed %CDR versus predicted DT (Fig-8) shows straight line. Therefore, we can conclude that the equation has good predictive ability.

Table-6: Regression analysis of % CDR (Y_2)

R square	0.97
Adjusted R square	0.93
Co-efficient	P value
$\beta_0 = 91.59$	-
$\beta_1 = 0.24$	0.55
$\beta_2 = 3.71$	0.0021
$\beta_{12} = 0.0000$	1.000
$\beta_1^2 = -2.02$	0.05
$\beta_2^2 = -1.73$	0.07

Regression coefficients, statistically insignificant ($p > 0.05$)

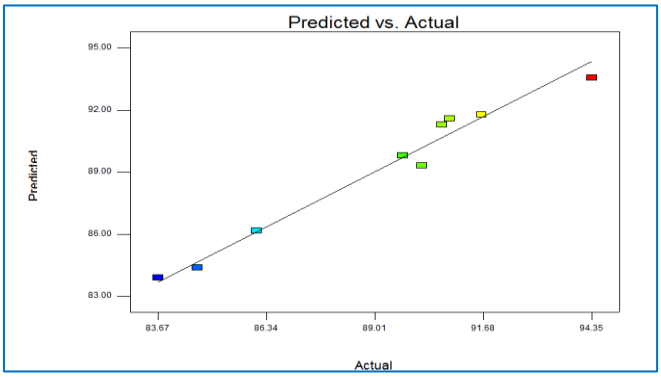

Fig-8: Predicted vs. actual plot (Y_2)

From the viewpoint of QbD, it is concluded that the factor X_2 (concentration of SLS) was a critical formulation variable for preparing the film with desirable characteristic of %CDR. It may be concluded that X_2 had positive effect on %CDR, which indicated that as the SLS concentration was increased, %CDR was increased.

The best way to look at the output is to draw 2D contour plot. The contour plot of % CDR reveals non-linearity Fig-9.

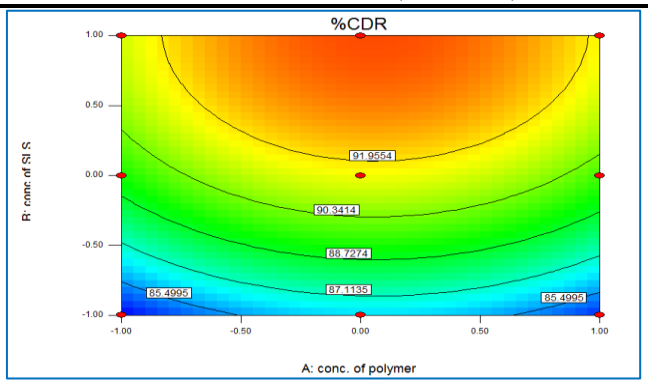

Fig-9: Contour plot for influence of various level of polymer on %CDR

The Fig-10 shows 3D response surface plot between X_1 and X_2 is non-linear in nature and highest response is seen with high (+1) level of concentration of SLS and low response was seen with low level (-1) of concentration of SLS. It may also be concluded that with change in concentration of SLS with significant change on %CDR was observed, whereas the concentration of HEC causes less influence on %CDR.

Folding endurance (Y_3)

The equations representing the quantitative effect of the formulation variables on folding endurance is shown in Table-7.

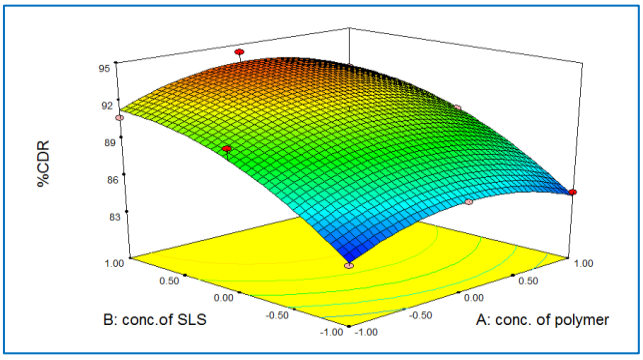

Fig-10: Response surface plot for influence of various levels of HEC and SLS on %CDR

Table-7: Regression analysis of folding endurance (Y_3)

R square	0.997
Adjusted R square	0.993
Coefficients	P value
$\beta_0 = 255$	-
$\beta_1 = 6.50$	0.006
$\beta_2 = 0.67$	0.210
$\beta_{12} = 0.00$	1.000
$\beta_1^2 = -24.50$	<0.001
$\beta_2^2 = 0.00$	1.000

Regression coefficients, statistically insignificant ($p > 0.05$)

The full model equation representing the quantitative effect of independent variables on folding endurance is:

Folding endurance (Y_3) = $255 + 6.50X_1 + 0.67X_2 - 24.50X_1^2$

The value of R^2 was found to be 0.997. The factor X_2, X_1X_2 interaction and polynomial term X_2^2 showed $p>0.05$ and therefore it was omitted from the full model shown above. The reduced or the refined model is shown below:

Folding endurance (Y_3) = $255 + 6.50X_1 - 24.50X_1^2$

The plot of observed folding endurance versus predicted folding endurance shown in Fig-11 as straight line. Therefore, it may be concluded that the equation has good predictive ability.

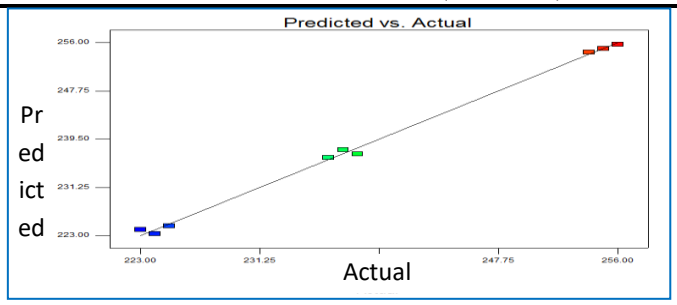

Fig-11: Predicted vs. actual plot (Y_3)

From the viewpoint of QbD, it was concluded that the factor X_1 (concentration of HEC) was a critical formulation variable for preparing the film with desirable characteristic of folding endurance. It may be concluded that X_1 have positive effect on folding endurance. The best way to look at the output is to draw 2D contour plot. The contour plot of folding endurance reveal linearity, as depicted in Fig-12.

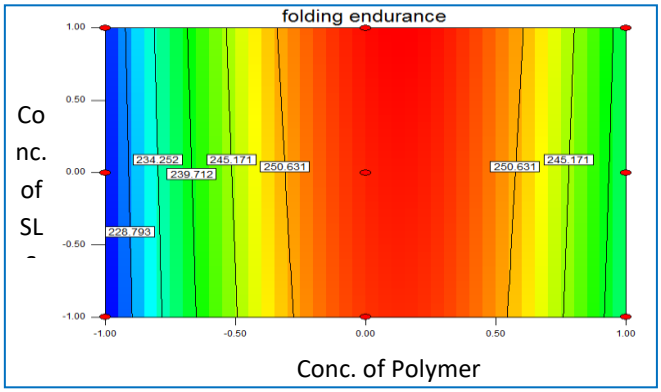

Fig-12: Contour plot for influence of various level of polymer concentration on folding endurance

The Fig-13 shows 3D response surface plot between X_1 and X_2 is non-linear in nature and highest response is seen with high (+1) level of concentration of HEC and low response is seen with low level (-1) of concentration of HEC. It can also be concluded that with change in concentration of HEC with significant change on folding endurance is observed, whereas the concentration of SLS causes less influence on folding endurance.

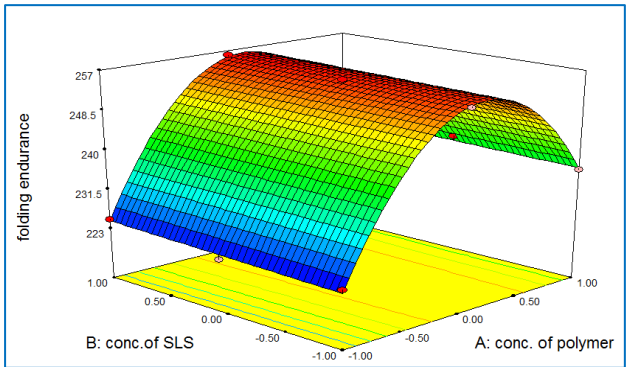

Fig-13: Response surface plot for influence of various level polymers on folding endurance

Here result showed that data of dependent variable, %CDR and folding endurance lies in optimized region, as seen in Fig-14. So, X_1 (concentration of HEC) and X_2 (concentration of SLS) in concentration of 1.9 %w/v and 0.96 %w/v respectively gives significant desired results.

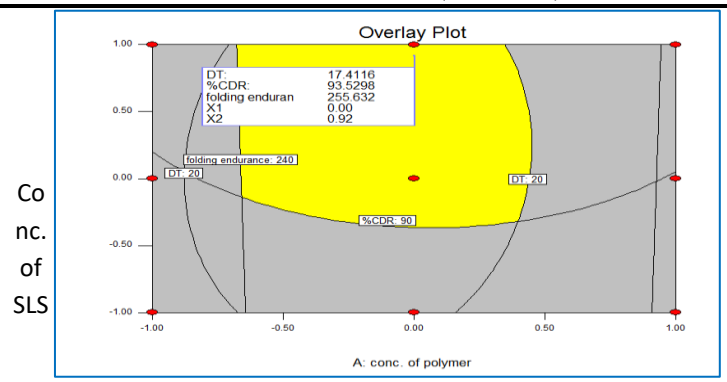

Fig-14: Overlay plot

Formulation of checkpoint batches for validity of models

Table-8: Comparison between predicted and experimental values of checkpoint batches

Batch	Responses	Predicted value	Experimental value	Relative error (%)
OF1	Disintegrating time (sec)	17.411	17.193	1.25
	% CDR	93.529	93.483	0.049
	Folding endurance	255.632	254.861	0.301
OF2	Disintegrating time (sec)	17.82	17.69	0.729
	% CDR	93.55	93.53	0.021
	Folding endurance	255.97	255.94	0.011
OF3	Disintegrating time (sec)	18.09	17.96	0.718
	% CDR	93.53	93.42	0.117
	Folding endurance	256.05	256.12	-0.002

Table-9: Evaluation parameters for check point batches

Batch	Thickness[#] (mm)	Folding endurance[#]	Disintegration time[#] (sec)	% Content uniformity[#]
OF1	0.084±0.0010	254±0.025	19±0.056	97.54±0.81
OF2	0.093±0.0011	223±0.683	22±0.577	96.48±0.93
OF3	0.067±0.0015	256±0.507	16±0.039	98.83±0.51
OF4	0.113±0.0057	238±0.062	28±0.24	95.61±0.31
OF5	0.090±0.0010	237±0.076	32±0.063	97.28±0.51
OF6	0.074±0.0020	255±0.043	17±0.569	98.70±0.62
OF7	0.069±0.0005	224±0.462	23±0.672	96.65±1.02
OF8	0.116±0.015	236±5.033	34±0.073	98.84±0.31
OF9	0.083±0.002	224±1.00	24±0.547	95.17±0.51

[#]mean ± SD (n=3)

Table-10: Data of Tensile strength

Parameters	Value
Trigger point	5 gm
Target value	200 gm
Test speed	30 mm/min
Peak load	156 gm
Tensile strength	32.66 N/mm^2

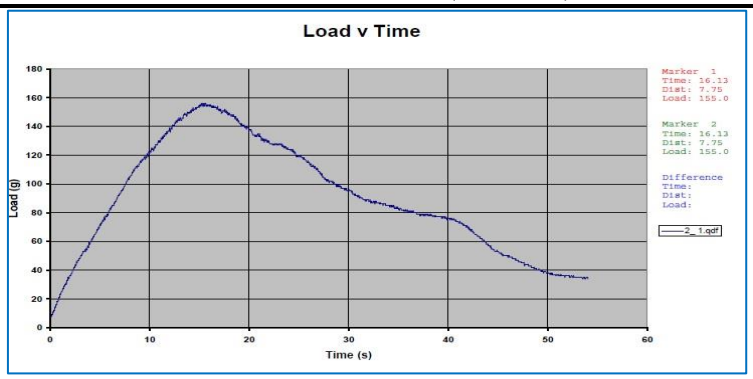

Fig-15: Graph for load vs time

In- vitro dissolution study of all films was carried out in phosphate buffer (pH 6.8) as a dissolution medium in modified oral cavity apparatus. The results obtained in the in vitro drug release study of ondansetron hydrochloride films containing HEC (OF1 to OF9) were in the range of 83.67% to 94.35%.

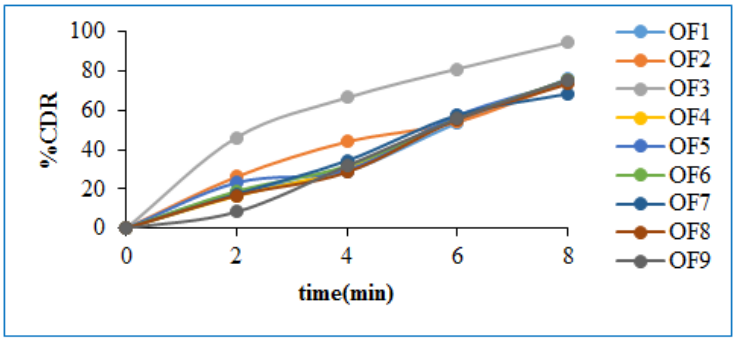

Fig-16: Percentage CDR of prepared batches

Table-11: Composition of 3_2 Factorial design of ondansetron hydrochloride film containing HEC

Independent variables			Levels		
			-1 (Low)	0 (Medium)	+1 (High)
Amount of HEC (%)			1.7	1.9	2.1
Amount of SLS (%)			0	0.5	1
Batch	**Variables**		**Response values**		
	X_1	X_2	Y_1	Y_2	Y_3
OF1	0	-1	19	86.1	254
OF2	-1	0	22	90.17	223
OF3	0	1	16	94.35	256
OF4	1	0	28	89.69	238
OF5	1	1	32	91.63	237
OF6	0	0	18	90.85	255
OF7	-1	-1	23	83.67	224
OF8	1	-1	34	84.64	236
OF9	-1	1	24	90.66	225

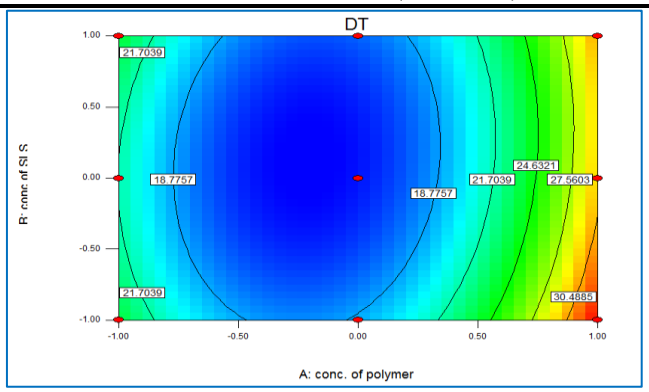

Fig-17: Contour plot showing the relationship between various level of concentration of polymer & concentration of SLS on DT

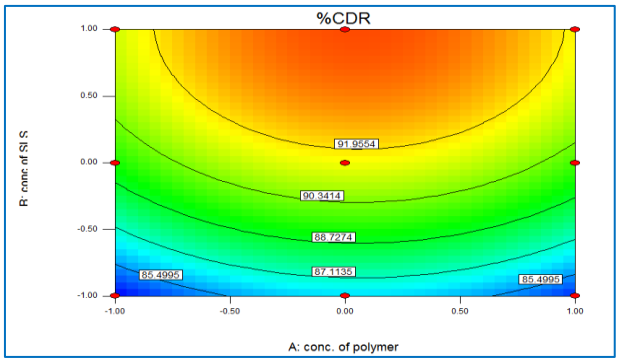

Fig-18: Contour plot showing the relationship between various level of concentration of polymer & concentration of SLS on %CDR

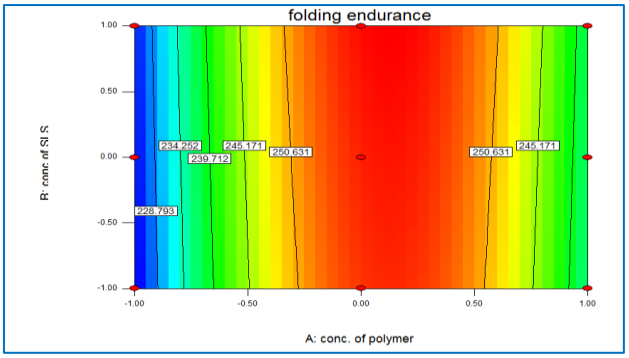

Fig-19: Contour plot showing the relationship between various level of concentration of polymer & concentration of SLS on folding endurance

Artificial neural network (ANN)

In an artificial neural network, the data is handled like a human brain wherein neurons play a key role. In ANN software also artificial neutrons try to simulate the work of a human brain. The computations are done in ANN by simulations. The procedure is very complex and hence requires specially developed computer software. Manual computation is not feasible. The training data set (a couple of data points are picked up from the experimental runs) is used to develop a mathematical model and thereafter test data (the data points not included in training) are uploaded for prediction. Finally, in ANN also we have the observed value of response and computed values of the selected response. The difference between the two responses is expressed as root mean square of error (RMSE). If the model is perfect, the value of RMSE is zero. Low value of RMSE is an indication of better fit. The data collected by us were charged in the Neurosolution software (version 7.0.0) and for each response ANN was run to get the values of RMSE. The values of RMSE are recorded in the table given below. The results reveal that the values are small in nature [67].

Table-12: Comparison of RMSE values of DoE and ANN

Response	RMSE (DoE)-EXCEL	RMSE (ANN)
1	7.71	$1.14*10^{-24}$
2	4.4	0.0606
3	17.06	0.3872

The input data set was also run in EXCEL software and the values of RMSE were obtained from the results of ANOVA. The results indicate that the values of RMSE are much larger. If the value of RMSE is high, predictive ability is less. If the mathematical model. This may happen if the true mathematical model is complicated in nature (i.e. when the polynomial terms (X^n) are statistically significant in nature). The higher value of RMSE in DoE indicate that ANN model possess better predictive ability. It is finally concluded for the linear models, incorporating only the main terms, DoE and ANN gives almost the same answers of RMSE. However, for the complicated model, as in the case of our study, ANN has an edge over DoE. The other results of ANN are represented in graphical and tabular form.

Response Y1

The number of epochs needed by the various options and the MSE values for Y_1 response summarized in the following table.

Table-13: Table containing RMSE values and No. of Epochs for Y_1 response

Function/ Parameter	RMSE	No. of Epoch
Tanh Axon	$1.14*10^{-24}$	25
Sigmoid Axon	0.6472	988
Linear Tan Axon	0.0606	31
Linear Sigmoid Axon	0.7602	785
Bias Axon	0.3356	5
Linear Axon	0.3356	5
Axon	0.3432	5

The graph shown above indicates that the Tanh Axon function using multilinear perception (MLP) showed the least RMSE value for Y_1 response. Twenty-five epoch were required by the software to arrive at the minimum mean square of error of 1.14×10^{-24} when Tanh Axon option was selected in the software. The value of MSE is very close to zero. When the observed value of a response and a calculated value of response are exactly identical MSE is equal to zero. It means that the fit is perfect (predicted value is very close to the observed value). The software generally achieves this by an iteration technique.

ResponseY_2

The number of epochs needed by the various options and the MSE values for Y_2 response summarized in the following table.

Table-14: Table containing RMSE values and No. of Epochs for Y_2 response

Function/ Parameter	RMSE	No. of Epoch
Tanh Axon	0.0632	17
Sigmoid Axon	0.6726	908
Linear Tan Axon	0.0606	12
Linear Sigmoid Axon	0.7045	527
Bias Axon	0.1686	5
Linear Axon	0.1686	6
Axon	0.1612	5

The graph shown above indicate that the Linear Tan Axon function using Multi linear perception (MLP) showed the least RMSE value for Y_1 response. Twelve epoch were required by the software to arrive at the minimum mean square of error of 0.0606 when Linear Tan Axon option was selected in the software. The value of MSE is very close to zero. When the observed value of a response and a calculated value of response are exactly identical MSE is equal to zero. It means that the fit is perfect (predicted value is very close to the observed value). The software generally achieves this by an iteration technique.

Response Y_3

The number of epochs needed by the various options and the MSE values for Y_3 response summarized in the following table.

Table-15: Table containing RMSE values and No. of Epochs for Y_3 response

Function/ Parameter	RMSE	No. of Epoch
Tanh Axon	0.0692	20
Sigmoid Axon	0.5551	744
Linear Tan Axon	0.3872	183
Linear Sigmoid Axon	0.7525	745
Bias Axon	0.4455	4
Linear Axon	0.4455	5
Axon	0.4472	5

The graph shown above indicates that the Tanh Axon function using multilinear perception (MLP) showed the least RMSE value for Y_1 response. Seventeen epochs were required by the software to arrive at the minimum mean square of error of 0.0692 when Tanh Axon option was selected in the software. The value of MSE is very close to zero. When the observed value of a response and a calculated value of response are exactly identical MSE is equal to zero. It means that the fit is perfect (predicted value is very close to the observed value). The software generally achieves this by an iteration technique.

Comparison of dissolution profile of optimized film and marketed film

Film formulation containing ondansetron hydrochloride and marketed formulation were studied for drug release profiles in phosphate buffer (pH 6.8), using modified oral cavity apparatus. Samples were withdrawn at predetermined time intervals with fresh media replacement and analyzed spectrophotometrically using UV visible spectrophotometer. Dissolution study was carried out of optimized formulation of ondansetron hydrochloride with marketed formulation of ondansetron hydrochloride. Optimized formulation showed nearly 93.48 % release of drug within 8 minutes. Nearly, 91.42 % of drug was released in 8 min in case of the marketed formulation. Percentage drug release of marketed formulation was found somewhat less in compared to the optimized prepared formulation. Result of dissolution profile of the marketed and optimized prepared formulation are shown in Fig-20.

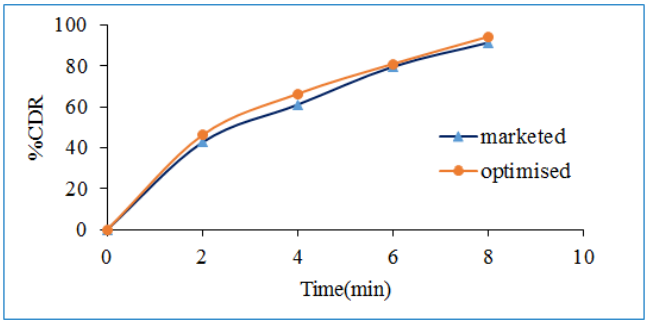

Fig-20: Comparison with marketed formulation

CONCLUSION

The fast dissolving oral film Ondansetron hydrochloride obtained by the solvent casting method showed acceptable mechanical properties and satisfactory drug release. The prepared film was transparent with smooth surface without any drug excipients interaction. The taste masking approach (sandwich technology) can be extended to other formulations also. The multiple regression analysis of the results led to be equations that describe adequately the influence of the selected variables, concentration of HEC and concentration of SLS on the responses under study. The desirability function led to the optimum values of the factors at which the produced film showed optimum DT and suitable mechanical properties. The high % drug release of the film was obtained in pH 6.8 phosphate buffer. This is expected to be correlated with quick onset of action. From the present work, it can be concluded that OFDF formulation can be a potential novel drug dosage form for geriatric and pediatric population and also for general population with enhanced patient compliance.

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