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Formulation and In-vitro Evaluation of Orodispersible Film of Torsemide

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ABSTRACT:

The present study is aimed at developing Orodispersible film of Torsemide using solvent casting method. Films were prepared by Solvent casting technique using HPMC E15 (Polymer), PEG 400 (Plasticizer), Crosscarmelose sodium (Super disintegrating agent), and sodium saccharin (Sweetener). FTIR Spectra showed absence of incompatibility between drug and excipients. A 3^2 full factorial design was applied to investigate the combined effect of the two independent formulation variables i.e., concentration of polymer (X_1), concentration of plasticizer (X_2) on the dependent variables i.e., Folding endurance (Y_1), disintegration time (Y_2), %CDR at 1 min (Y_3) and %CDR at 2 min (Y_4). Results of the multiple regression analysis revealed that the independent variables significantly affected the dependent variables. The optimum batch was identified. The Check point batch was formulated using HPMC E15 (292 mg), PEG 400 (20% of polymer concentration) and 20 mg of CCS. The theoretical and practical results were similar which confirm the prediction power of model. The stability study of optimized batch was carried out at 40 ± 0.5°C temperature and 75 ± % 5 RH for one month. It showed no statistically significant difference in disintegration time, folding endurance, drug content and dissolution profile before and after stability study. The optimized Orodispersible film of Torsemide can be a promising dosage form for the treatment of poisoning.

KEY WORDS: Orodispersible film, Torsemide, Diuretic, Poisoning, factorial design

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INTRODUCTION:

Recent advances in the technology of pharmaceutical dosage forms have offered worthwhile dosage choices from oral route for pediatrics, geriatric, bedridden, nauseous or non- cooperative patients (1). A vast diversity of pharmaceutical research is focused at evolving new dosage forms. Most of these labors have concentrated on either formulating novel drug delivery systems or improving the patient compliance. Orodispersible film should be prepared to avoiding hindrance of patient noncompliance (2). Orodispersible film, a relatively new drug delivery system in which thin film was prepared that facilitate delivery of the drugs to oral cavity, was developed based on the technology of the transdermal patch (3). The Orodispersible film consists of a very thin strip made up of hydrophilic polymer, which is just placed on the patient's tongue or any oral mucosal tissue, promptly wet by saliva the Orodispersible film adsorb saliva and quickly hydrates (4). It then rapidly disintegrates and dissolves to release the medication in oral cavity (5). Drug absorption through oral mucosa and directly pass into systemic circulation (6, 7).

Torsemide is a selective inhibitor of inhibits the $Na^+/K^+/2Cl^-$-carrier system extensively used for the treatment of acute poisoning (8, 9, 10), acute renal failure, edema, hypertension, congestive heart failure and hepatic disorder (11,12). The main intentions of the present study were to prepare and evaluate the Orodispersible film of Torsemide and to study the different formulation variables that affect the drug release (13, 14).

MATERIALS AND METHODS

Materials: Torsemide was obtained as a gift sample from purechem private Laboratories, Ankleshwer; Gujarat, India. HPMC E5, E15, E50, and PVP K30 were obtained from Lupin Research Park (Lupin Ltd). PEG 400, glycerol, Sodium saccharin, PVA, CCS and SSG was obtained from Research Lab Fine Chem Industries, Mumbai, India. All chemicals used were of analytical grade and were used without further purification. Deionized distilled water was used throughout the study.

Method

Preparation of the Torsemide containing Orodispersible films

The Torsemide orodispersible films were prepared by solvent casting method (15). solution 1 was prepared by dissolving in 6 mL ethanol at 40°C with stirring polymer, superdisintegrant and sodium saccharin, was allowed to stir for 5 min on magnetic stirrer (16). Solution 2 Torsemide has been dissolved in 3 ml 0.1N NaOH and 8 ml ethanol using 1 % Tween 80. This mixture was then added to the aqueous viscous solution. PEG was added lastly and stirred for 40min. Then the mixture solution was casted as a film onto a glass petridis and it was dried at room temperature for 6 h. The film was carefully removed from the Petridis, checked for any imperfections, and cut into the 3 cm×2 cm in size. The film was stored in aluminum foil tills further use (17). Drug excipient stability was carried out using FTIR.

Evaluation of Orodispersible Films

Thickness of the film:

Thickness of film was measured by Venire calipers. Thickness measured at different strategic locations. Thickness is directly related to the accuracy of dose in film so that it is essential to determine uniformity in the thickness of the film. The thickness of the film depends on the concentration of the polymer (18).

Tensile strength:

Tensile strength of the film can be determined by digital tensile tester. Tensile tester consists of two load cell grips. The lower cell grip is fixed and upper cell grip is movable. The test film of 3×2 cm can be fixed between lower and upper cell grips and force will be slowly applied till the film breaks. Results of tensile strength in kg/cm^2 or N/cm^2 will be taken (18).

$$\text{Tensile strength} = \frac{\text{Load at failure} * 100}{\text{Strip Thickness} * \text{Strip Width}}$$

Folding endurance:

The folding endurance is measured by manually. Folding endurance is determine by repeat folding of film at the same plane till film specimen breaks. Number of times of film is folded at the same plain deprived of breaking referred to folding endurance. This gives a suggestion of brittleness of the film. A small strip of 3×2 cm was subjected to this test by folding the film at the same plane repeatedly several times until a visible crack was observed and the results are taken (18).

Disintegration time:

In vitro disintegration time is determined visually film sample placed in a Petridis of 25 ml salivary fluid and observed time till complete break. The disintegration time is the time when the film starts to break or disintegrates (19).

Uniformity of drug content:

For determining the uniformity of drug content in the film at least three films (3x2 cm^2) were cut from different section of the film and drug content was calculated for all three films using the same procedure as mentioned in drug content. The drug content of all three strips was compared. Same procedure was repeated for all the nine batches (20).

In vitro Drug Release

Dissolution study was carried out in USP type II paddle apparatus using 300 ml stimulated salivary fluid (pH 6.8) as a dissolution medium and rotated at 50 rotations per minute. 5 ml aliquots were withdrawn at different time intervals and same amount of fresh dissolution medium

was added. The specimens were assayed for drug content at 287 nm wavelength using UV-spectrophotometer. The cumulative percentage drug release was calculated.

Surface pH study

The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 30 s. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing Equilibration for 1 min. The average of three determinations for each formulation was done (21).

Stability study

The stability study is performed to check physical and chemical integrity of the formulation, generally carried out through optimized batch Storage condition 40^{o}c ± 0.5^{o}C at 75 ± 5 % RH Time period 1 month, the films were visually examined for any physical changes, changes in drug content and *in vitro* disintegration time.

RESULTS AND DISCUSSION

Selection of polymer

Different types of polymer, utilized for the selection of polymers, were Poly vinyl alcohol (PVA), Polyvinyl pyrrolidone K-30 (PVP K-30), different grades of Hydroxypropyl methylcellulose (HPMC), mixture of different grades of Hydroxy propyl methylcellulose. Selection parameters taken into consideration were disintegration time, seperability and folding endurance. The HPMC E15 has shown better film forming property than other grades of HPMC, PVA, PVP K-30 alone and combination of HPMC by considering the parameters like separability, folding endurance, and disintegration rate (data not shown). Therefore the film with HPMC E15 taken into consideration for further studies.

Selection of plasticizer

Glycerol and Polyethylene Glycol 400 (PEG-400) were utilized for the selection of the good plasticizer system. Selection was done on basis of stickiness and folding endurance. PEG 400 is better plasticizer than Glycerol (data not shown). So, it was selected as plasticizer.

Selection of super disintegrating agents

Sodium starch glycolate (SSG) and Crosscarmelose sodium were utilized for the selection of the good super disintegrator. Selection of CCS was done on the basis of disintegration time (in seconds). From Sodium starch glycolate (SSG) and Crosscarmelose sodium (CCS), CCS had good effect (data not shown). Thus it gave the edges to CCS for the selection as super disintegrant.

Drug excipients compatibility study

Drug excipient compatibility using FTIR

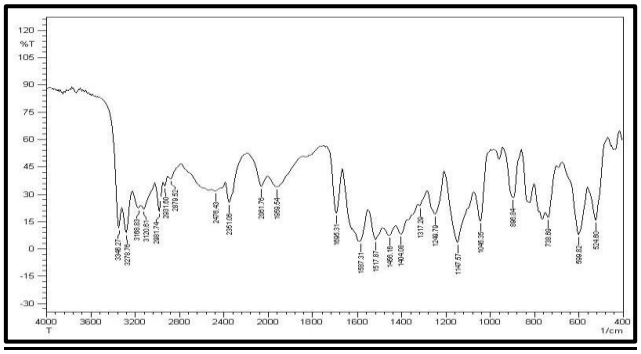


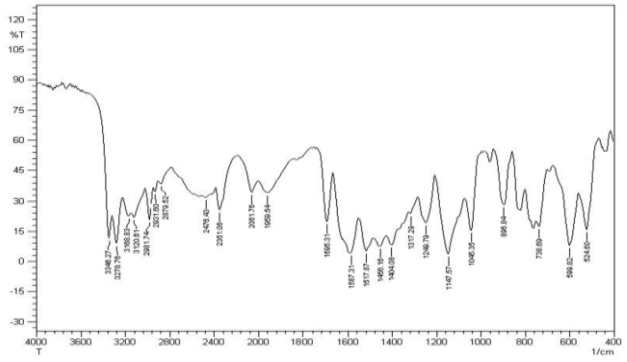
Figure 1 FTIR spectra of pure Torsemide

Table 1 Interpretation of FTIR

Sr No	Functional group	Observed frequency cm^{-}	Reported frequency cm^{-}
1	C= N	1695.31	1697.42
2	C–N	1249.79	1282.15
3	Hetero atoms	3278.76	3279.94

The major peaks for the pure drug were observed at 1697.42.31cm-1 (C= N stretch), 1282.15 cm-1 (C-N stretch) and 3279.94 cm-1 for of hetero atoms (table 1).

A



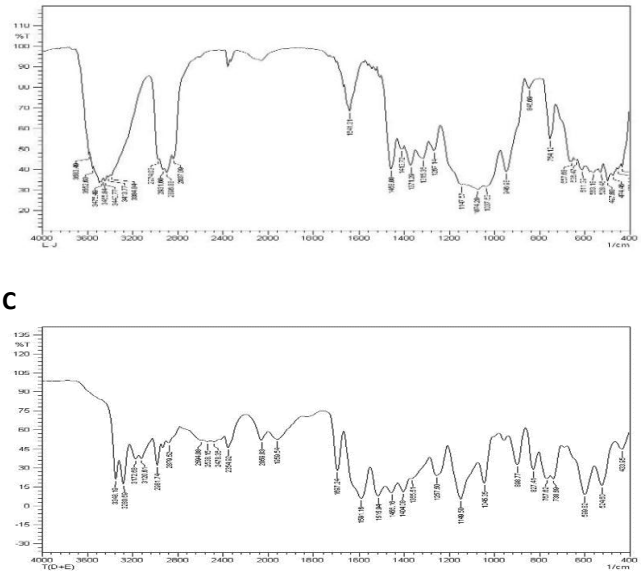


Figure 2 A=FTIR spectra of pure Torsemide, B= FTIR spectra of HPMC E15, C=FTIR spectra of physical mixture of Torsemide and HPMC E15

Results of FTIR figures 2 showed that the major peak of drug remain same, it was found that there was no interference of excipient used in the formulations. Drug and excipients are compatible.

Selection of factors, levels and responses of 3^2 full factorial design

It is desirable to develop an acceptable pharmaceutical formulation in shortest possible time using minimum number of man-hours and raw materials. Traditionally pharmaceutical formulations developed by changing one variable at a time approach. The method is time consuming in nature and requires a lot of imaginative efforts.

Moreover, it may be difficult to develop an ideal formulation using this classical technique since the joint effects of independent variables are not considered. It is therefore very essential to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial design (21).

A 3^2 full factorial design was used for optimization of ODF formulation. The two factors (Concentration of plasticizer and Concentration of polymer), each at three levels -1, 0 and +1(200, 300 and 400) were taken as independent variable (Concentration of plasticizer (x_1) and Concentration of polymer (x_2).The dependent variable selected were Folding endurance (y_1),Disintegration time (y_2) and cumulative drug release at 1min.(Y_3) and 2min.(Y_4). Table summarizes nine various film formulations X_1 plasticized with X_2 per 3^2 full factorial design. Design expert software 10.0.0, used for obtaining correlation between independent variable with selected dependent variable.

After selection of various levels and factors, all the batches of Torsemide mouth dissolving films were prepared. Formulas for all the batches are given in Table 2. The prepared formulations were evaluated for drug content, tensile strength, folding endurance, *In vitro* drug release, appearance, thickness, disintegration time, surface pH.

Table 2 Formulation of Batches according to 3^2 full factorial design

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Torsemide(mg)	106	106	106	106	106	106	106	106	106
HPMC E15 (mg)	200	300	400	200	300	400	200	300	400
PEG 400 (% of polymer)	10	10	10	15	15	15	20	20	20
CCS(mg)	20	20	20	20	20	20	20	20	20
Tween 80 (%)	1	1	1	1	1	1	1	1	1
Sodium saccharin (mg)	5	5	5	5	5	5	5	5	5
Ethanol(ml)	14	14	14	14	14	14	14	14	14
NaOH 0.1N(ml)	3	3	3	3	3	3	3	3	3

Table 3 Characterization of Orodispersible film of torsemide

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness(mm)	0.11	0.13	0.14	0.12	0.13	0.15	0.11	0.14	0.15
Folding endurance	187	269	308	226	285	331	303	343	386
Tensile strength(N/cm^2)	1.18	1.29	1.37	1.15	1.28	1.35	1.13	1.27	1.34
Disintegration time(Sec)	30	42	51	27	35	45	25	29	41
Drug content(mg)	9.89	9.94	9.93	9.87	9.92	9.81	9.96	9.98	9.97
Surface pH	6.8	7.2	7.4	6.9	7.1	7.3	6.8	7.3	7.5
CDR at 1 min.	59.12	60.32	35.12	65.52	64.72	37.12	69.52	71.52	40.32
CDR at 2 min.	98.91	99.33	68.69	97.81	97.50	70.14	95.08	99.11	64.19

In vitro Drug Release

In vitro drug release was performed in 300 ml simulated saliva fluid pH 6.8 as dissolution medium maintained at 37 ± 0.5 ^{o} C and stirred at 50 rpm using USP type II apparatus (22).

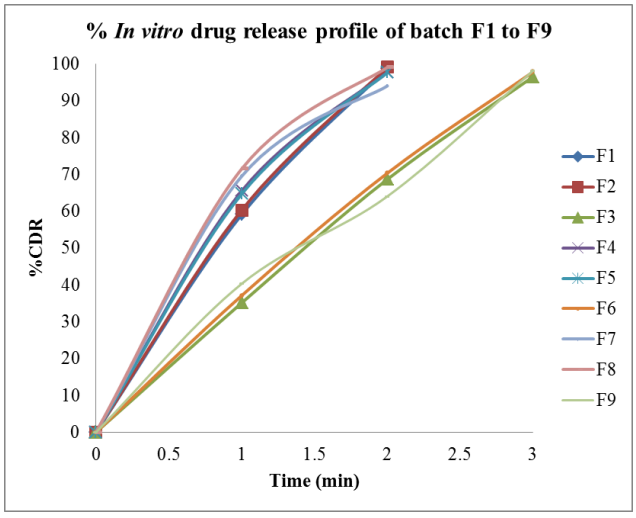


Figure: 3 % *In vitro* drug release profile of batch F1 to F9

Effect of independent variables on folding endurance (Y_1)

Folding endurance varies 187 to 386 from batch F1 to F9.

The following equation was generated when folding endurance correlated with independent variable (X_1 and X_2).

Folding endurance (Y_1) = 293.11 + 51.50* X_1+ 44.67 * X_2(1)

(R^2=0.9522, Linear model)In this case X_1, X_2 are significant model terms.

In the above Equation 1, positive sign signifies synergistic influence of coefficient on response variables. From the above equation it was evident that polymer concentration and plasticizer concentration both have influence on folding endurance. The enhancement in concentration of polymer and plasticizer in films enhance folding endurance (23). The X1 has more significant effect on folding endurance the X2. The contour and response surface plots are shown in Figure 4 and Figure 5, which confirmed the effect of dependent variables on folding endurance.

Table 4 Model Summary Statistics

Source	Std. Dev.	R-Squared	Adjusted R-Squared	Predicted R-Squared	PRESS	
Linear	15.27	0.9522	0.9363	0.8894	3239.49	Suggested
2FI	14.41	0.9646	0.9433	0.9055	2765.83	
Quadratic	7.85	0.9937	0.9832	0.9240	2226.81	
Cubic	2.33	0.9998	0.9985	0.9661	992.25	Aliased

Table 5 Analysis of variance table for folding endurance

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Coefficient Estimate
Model	27884.17	2	13942.08	59.81	0.0001	293.11
A-Concentration of Polymer	15913.50	1	15913.50	68.26	0.0002	51.50
B-Concentration of plasticizer	11970.67	1	11970.67	51.35	0.0004	44.67
Residual	1398.72	6	233.12			
Cor Total	29282.89	8				

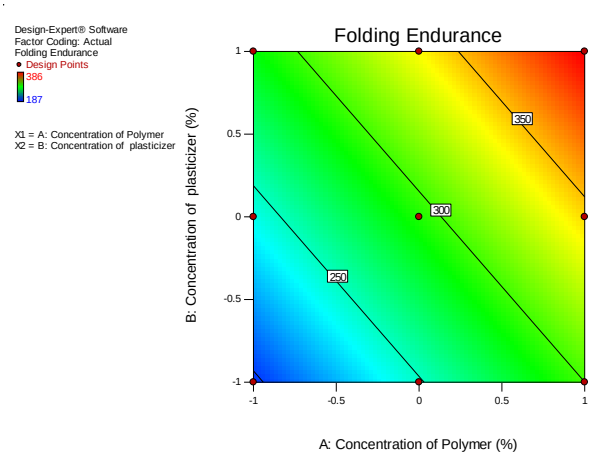


Figure 4 counter plot of response folding endurance

Effect of independent variables on Disintegration time (Y_2)

Disintegration time was 25 seconds to 52 seconds.

Disintegration time = 36.22 + 9.33 * X1 -4.83 * X2 (2)

(R2 = 0.9669, Liner model). In this case X1 ,X2 are significant model terms.

In the above equation (2), positive sign signifies synergistic influence of coefficient on response variables. The negative sign in the above equation reflect the inverse correlation of that coefficient/variable with response. From the above equation it was evident that polymer concentration and plasticizer concentration both influence on disintegration time. The increase in concentration of X1, in film increases disintegration time (24). The increase in concentration of X2, in film decreases disintegration time. The contour and response surface plots are shown in Figure 6 and Figure 7, which confirmed the effect of dependent variables on disintegration time.

Table 6 Model Summary Statistics

Source	Std. Dev.	R-Squared	Adjusted R-Squared	Predicted R-Squared	PRESS	
Linear	1.95	0.9669	0.9558	0.9103	61.52	Suggested
2FI	1.66	0.9800	0.9680	0.8950	72.02	
Quadratic	1.71	0.9872	0.9659	0.8447	106.48	
Cubic	0.33	0.9998	0.9987	0.9705	20.25	Aliased

Table 7 Analysis of variance table for Disintegration time

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F	Coefficient Estimate
Model	662.83	2	331.42	87.51	< 0.0001	36.22
A-Concentration of Polymer	522.67	1	522.67	138.01	< 0.0001	9.33
B-Concentration of plasticizer	140.17	1	140.17	37.01	0.0009	-4.83
Residual	22.72	6	3.79			
Cor Total	685.56	8				

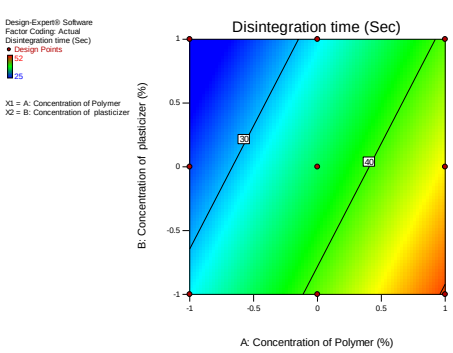


Figure 5 counter plot of response folding endurance

The % CDR at 1 min varies 35.12 to 71.72 from batch F1 to F9.

Table 8 Model Summary Statistics

Source	Std. Dev.	R-Squared	Adjusted R-Squared	Predicted R-Squared	PRESS	
Linear	8.51	0.7397	0.6529	0.4463	924.49	
2FI	9.24	0.7440	0.5905	0.0136	1646.84	
Quadratic	1.50	0.9960	0.9892	0.9543	76.38	Suggested
Cubic	1.10	0.9993	0.9942	0.8679	220.52	Aliased

Effect of independent variables on %CDR at 1 min (Y_3)

Table 9 Analysis of variance table for %CDR at 1 min

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F	Coefficient Estimate
Model	1662.78	5	332.56	148.10	0.0009	65.45
A-Concentration of Polymer	1115.21	1	1115.21	496.63	0.0002	-13.63
B-Concentration of plasticizer	119.71	1	119.71	53.31	0.0053	4.47
AB	7.29	1	7.29	3.25	0.1694	-1.35
A^2	420.50	1	420.50	187.26	0.0008	-14.50
B^2	0.080	1	0.080	0.036	0.8623	0.20
Residual	6.74	3	2.25			
Cor Total	1669.52	8				

$$\% \text{ CDR at 1 min} = 65.45 - 13.63 * X_1 + 4.47 * X_2 - 1.35 * X_1X_2 - 14.50 * X_1^2 + 0.20 * X_2^2 \quad (3)$$

(R^2= 0.9960, Quadratic model).

Equation 3 showed the effect of independent variables on %CDR at 1 min. Table 9 showed that theX_1, X_2 and X_1^2 are significant model terms (p value less than 0.05). In the above equation (3), positive sign signifies synergistic influence of coefficient on response variables. The negative sign in the above equation reflect the inverse correlation of that coefficient/variable with response (25). From the above equation it was evident that polymer concentration and plasticizer concentration both influence on disintegration time. The increase in concentration of X_1, in film decreases % CDR at 1 min. As the concentration of polymer in film increased the time required to release drug from the matrix of polymer increased (26, 27). Thus the %CDR at 1 min decreased. The increase in concentration of X_2, in film increases % CDR at 1 min. This is because as the concentration of plasticizer (PEG 400) increased the wettability of film increased and thus % CDR at 1 min increased. Here interactive term (X1X2) and quadratic term (X12 and X22) also showed significant effect on % CDR at 1 min. The contour and response surface plots are shown in Figure 8 and Figure 9, which confirmed the effect of dependent variables on % CDR at 1 min.

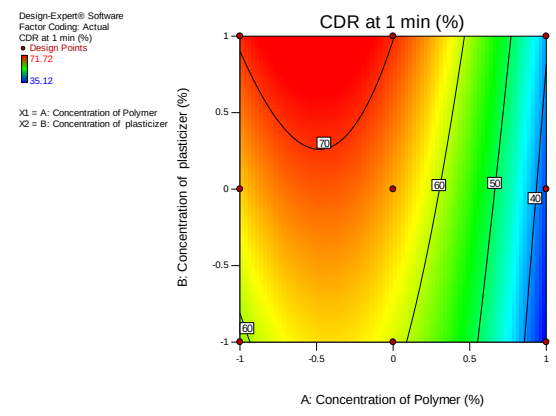


Figure 6 counter plot of response %CDR at 1 min

Effect of independent variables on %CDR at 2 min (Y_4) CDR at 2 min varies 64.19 to 99.33 from batch F1 to F9.

Table10 Model Summary Statistics

Source	Std. Dev.	R-Squared	Adjusted R-Squared	Predicted R-Squared	PRESS	
Linear	9.49	0.7105	0.6140	0.3684	1178.60	
2FI	10.39	0.7106	0.5369	-0.2467	2326.37	
Quadratic	2.24	0.9920	0.9786	0.9200	149.37	Suggested
Cubic	2.65	0.9962	0.9699	0.3133	1281.46	Aliased

Table 11 Analysis of variance table for %CDR at 2 min

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Co efficient
Model	1851.05	5	370.21	74.07	0.0024	99.27
A-Concentration of Polymer	1313.65	1	1313.65	262.84	0.0005	-14.80
B-Concentration of plasticizer	12.18	1	12.18	2.44	0.2164	-1.42
AB	0.11	1	0.11	0.022	0.8904	-0.17
A^2	523.37	1	523.37	104.72	0.0020	-16.18
B^2	1.74	1	1.74	0.35	0.5971	-0.93
Residual	14.99	3	5.00			
Cor Total	1866.04	8				

$$\text{CDR at 2 min} = 99.27 - 14.80 * X_1 - 1.42 * X_2 - 0.17 * X_1X_2 - 16.18 * X_1^2 - 0.93 * X_2^2 \quad (4)$$

(R^2 = 0.9920, Quadratic model). Table 11 showed that the X_1, $X_1^2$are significant model terms (p value less than 0.05).The negative sign in the above equation reflect the inverse correlation of that coefficient/variable with response. The increase in concentration of X_1, in filmsdecreases % CDR at 2 min. The contour and response surface plots are shown in Figure 10 and Figure 11, which confirmed the effect of dependent variables on % CDR at 2 min.

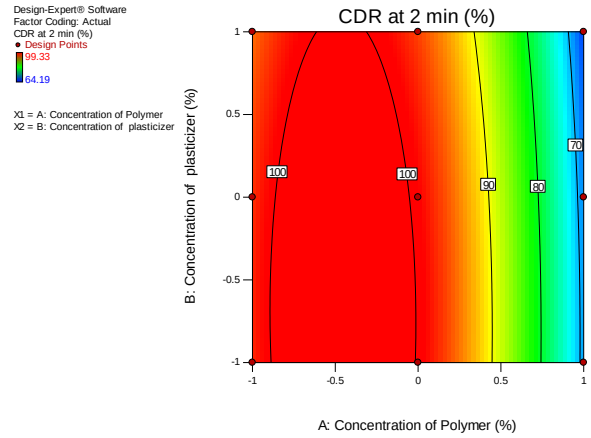


Figure 7 counter plot of response %CDR at 2 min

Optimization of formulation

The overlay plot of the responses generates an optimized area, as per the desired criteria (Maximum folding endurance, minimum disintegration time, maximum %CDR at 1 and 2 min).

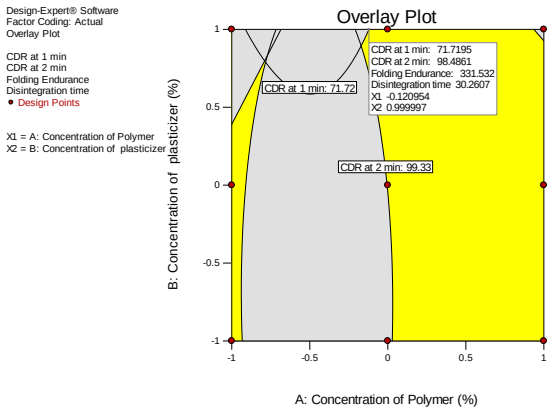


Figure 8 Overlay Plot of Response Variables

It can be concluded that by adopting a systemic formulation approach(Figure 12), one can reach to an optimum point in the shortest time with minimum efforts From the contour plot check point batch has been taken for the evaluation to see the accuracy of the optimization (28).

Meaning	Colored Zone of Overlay plot
All the responses meet the predefined criteria.	
One or more responses failed to meet the predefined criteria.	

Stability Study

The optimized formulation (Batch F10) was wrapped in aluminum foil and stored at 45 ± 0.5°C and 75 ± 5 % RH for period of one month (29). After the period of one month, film was tested for weight Uniformity of film, Thickness of film, Tensile strength, Folding endurance, Disintegration time, Content uniformity and *in vitro* drug release study, surface pH

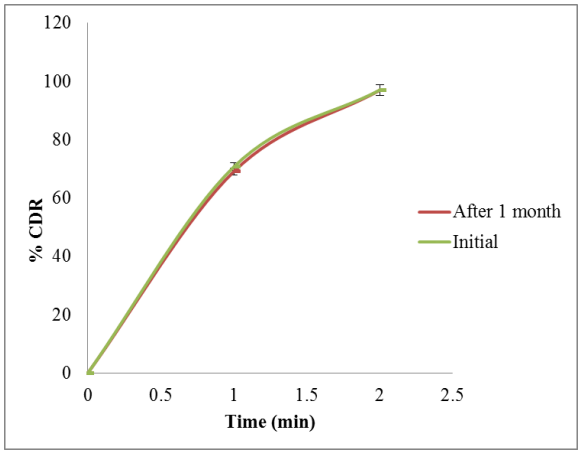


Figure 9 *In vitro* dissolution profile of optimized batch initial and after 1 month

Table 14 Evaluation of batch F10 initial and after 1 month (stability study)

Parameters	Initial	After 1 month
Appearance	Transparent	Transparent
Thickness(mm)	0.14	0.14
Folding endurance	327	321
Tensile Strength(N/mm^2)	1.28	1.27
Disintegration time (Sec)	28	30
Drug content	9.98	9.97
% CDR at 1 min	70.72	69.12
% CDR at 2 min	97.08	97.02

The result of evaluation before and after stability study (Table 15 and figure 14)

Indicated that the film remain stable during stability study.

Table 15 Paired t-Test

		Variable 1	*Variable 2*
Mean		83.07	83.9
Variance		389.205	347.4248
Observations		2	2
Pearson Correlation		1	
Hypothesized Difference	**Mean**	0	
Df		1	
t Stat		-1.07792	
P(T<=t) one-tail		0.238069	
t Critical one-tail		6.313752	
P(T<=t) two-tail		0.476138	
t Critical two-tail		12.7062	

The dosage form did not show any significant difference (t_{cac}< t_{tab})(table 15). The dissolution study showed (figure14) that there was no significant difference observed between the release pattern of film before and after stability study.

CONCLUSION

The orodispersible films of Torsemide were successfully formulated by Solvent casting technique. The optimized Torsemide orodispersible film showed satisfactory results with respect to disintegration time, drug release, mechanical strength and folding endurance. Thus we can predict better and faster drug delivery from film. The improved bioavailability, immediate onset of action and improved patient compliance can be achieved. The overall result of the study indicates that such fast dissolving system is an excellent drug delivery system for fast delivery of Torsemide in acute poisoning.

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