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FORMULATION AND EVALUATION OF ORAL FAST DISSOLVING FILM OF GABAPENTIN BY QBD APPROACH

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ABSTRACT

Objective: *The objective of the present investigation was to formulate, evaluate and optimize oral film of Gabapentin using experimental design (Box Behnken).* ***Methods:*** *Oral films of Gabapentin were formulated using HPMC E15 premium polymer as a film forming agent and propylene glycol as plasticizer and tween 80 as surfactant. The drug & excipients were characterized as per USP 2014. Oral dissolving films were prepared by solvent casting method and were optimized by using box behnken design (A three -factor, two level). Formulations were prepared using three independent variables namely polymer quantity(X_1), Plasticizer(X_2) and surfactant concentration(X_3), whereas disintegration time (Y_1) and % drug release (Y_2) as dependent variables. The formulations were prepared by solvent casting technique and were evaluated for in vitro dissolution studies. The stability studies of the films were performed for optimized batch as per ICH guideline. From the results of design batches, best batch was selected and evaluated for In-Vivo pharmacokinetic study in albino rat model.* ***Results:*** *Box Behnken Design using Design Expert Software was used to optimize and evaluate the main effects, interaction effects and quadratic effects of the formulation ingredients on the disintegration time & in vitro drug release. Films were characterized such as thickness, weight variation, appearance content uniformity, folding endurance, surface pH, in-vitro drug release, films were found to be satisfactory when evaluated for all parameters of the films was found to be neutral. The designs establish the role of the derived polynomial equation and contour plots in predicting the values of dependent variables for the preparation and optimization and examined In-Vivo study. The optimized batch is passed the accelerated stability studies. The statistically optimized formulation was characterized with UV, FT-IR (Fourier transformation-infrared spectroscopy) and DSC (differential scanning calorimetry) studies and found no chemical interactions between drug and polymer.* ***Conclusion:*** *In salivary pH the prepared fast dissolving films of Gabapentin could be a better alternative for achieving rapid oral bioavailability in treatment of neuropathic pain.*

KEY WORDS

Oral Film, Gabapentin, Box Behnken Design and Solvent Casting Technique, in-vivo study.

INTRODUCTION:

Gabapentin was first approved for use in 1993.The wholesale price is about US$ 1.35 per day. In the United States it has been available as a generic medication since 2004. As of 2015 the cost for a typical month of medication in the United States is US$100 to US$200. During the 1990s Parke-Davis, a sub-company of Pfizer used a number of techniques to encourage physicians in the United States to use gabapentin for unapproved uses.[1]

Gabapentin, marketed under the brand name Neurontin among others, is a medication used to

treat epilepsy, neuropathic pain, hot, flashes, and restless leg syndrome. In epilepsy it may be used for those with partial seizures.[2] It is recommended as one of a number of first line medications for the treatment of neuropathic pain in diabetic neuropathy, post-herpetic neuralgia, and central neuropathic pain. [6] For neuropathic pain about 14% of people have a meaningful benefit.

Common side effects include sleepiness and dizziness. Serious side effects may include an increased risk of suicide, aggressive behaviour, and drug reaction with eosinophilia and systemic symptoms. [4] It is unclear if it is safe during pregnancy or breast feeding. Lower doses should be used in people with kidney problems. Gabapentin does not affect the activity of the inhibitory neurotransmitter γ-amino butyric acid (GABA); how it works is unclear.[3]

The fast dissolving drug delivery system is a new drug delivery technique to provide medicine to such patients i.e. pediatric, children, geriatrics etc. Fast-dissolving films have acquired great importance in the pharmaceutical industry due to their unique properties & advantages. As the fast dissolving film utilizes sublingual route, rapid absorption of the drug is possible, which finally lead to quick onset of drug action.[4] Difficulty in swallowing is a common problem of all age group, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. Solid dosage form that can be disintegrated, dissolved, or suspended by saliva in the mouth resulting easy swallowing can provide significant benefits to the pediatric and geriatric population, as well as other patients who prefer the convenience of easily swallow able dosage form. In case of allergic condition rapid action of drug is required. The fast dissolving films fulfill the requirement of potential solid dosage form for levocetirizine in treating allergic conditions. It shows patient compliance, rapid on-set of action, increased bioavailability and good stability make this film popular as a dosage form of choice.

MATERIALS AND METHODS:

Materials

NAME	COMPANY
Gabapentin	Wockhardt pvt.Ltd, Aurangabad.
Hydroxy Propyl Methyl CelluloseE15	Research-lab fine chem. industries, Mumbai
Propylene Glycol	Meher chemie, Ratnakar Apt. Mumbai.
Tween 80	Ozone international, Mumbai.
Citric Acid	Research-lab fine chem. industries, Mumbai
Aspartame	Ozone international, Mumbai.
Menthol	Meher chemie, Ratnakar Apt. Mumbai.
Amaranth	Vishal chem. Mumbai 400002. India.
Water	-

Table No.1: list of ingredients with sources.

FORMULATION OF FILM:

Sr. No.	Ingredients	Quantity(mg)	Category
1.	Gabapentin	180	Anticonvulsant, Neuropathic pain
2.	Hydroxy Propyl Methyl CelluloseE15	300-400	Polymer
3.	Propylene Glycol	200-275	Plasticizer
4.	Tween 80	10-20	Surfactant
5.	Citric Acid	10	Saliva stimulating agent
6.	Aspartame	q.s	Sweetening agent
7.	Menthol	q.s	Flavoring agent
8.	Amaranth	q.s	Colouring agent
9.	Water	q.s	Vehicle

Table No.2: Formulation table of film.

METHODS:

Preparation of Gabapentin oral fast dissolving film:

Films were prepared by using different grades of hydroxyl propyl methyl cellulose by casting method (Lutfulkabir AK, 2009). HPMC E15 were used to formulate film and E15 was selected due to the less brittleness of the film. Then propylene glycol (20% of polymer) was selected as plasticizer due to its higher plasticity. Then tween 80 was selected as a surfactant of 15% of polymer due to more transparency. Thus the final formula was introduced, the formation of oral film (Gabapentin). The specified amount of HPMC E15 was weighed and dissolved in 10 ml of distilled water and an increase in the quantity of citric acid as a saliva stimulating agent, aspartame, menthol and tween 80 was added to the mixture under continuous stirring. And last 120 mg of the drug was dispersed in the mixture. The solution was kept under continuous stirring on a magnetic stirrer for 30 minutes. Then the solution was poured into the petridish and kept for 24 hours at room temperature for drying. The film was removed from the petridish, cut into 2×2 cm^2 size and preserved in aluminum foil and stored.

Fig. No.1: Photography of film of Gabapentin

Design of experiments:

Box–Behnken designs are experimental designs for response surface methodology devised by George E.P. Box and D. Behnken in 1960. The Box–Behnken design for three factors involves three blocks in each of which 3 factors are varied through the four possible combinations of high and low. It is necessary to include center points as well. A 3-factor, 3-level design used is suitable for exploring quadratic response surfaces and constructing polynomial models with Design Expert version 8.0.7.1 The three independent variables such as polymer (X1) and plasticizer (X2) and surfactant (X3) were selected on the basis of the preliminary studies carried out before the experimental design is being implemented. The experimental design was applied to investigate the effect of different independent variables such as X_1, X_2 and X_3.[13, 14]

$$Y= b_0+b_1X1+b_2X_2+b_{12}X_1X_2+b_{11}X^2_1+b_{22}X^2_2$$

Independent variables in design.

Factor	Level used, actual (coded)		
Independent variables	**Low (-1)**	**Medium (0)**	**High (+1)**
X1= Concentration of polymer (% w/w)	**300**	**350**	**400**
X2= Concentration of plasticizer (%w/w)	**200**	**237.5**	**275**
X3= Concentration of surfactant (%w/w)	**10**	**15**	**20**

X1= Concentration of polymer (% w/w).
X2 =Concentration of plasticizer (% w/w).
X3= concentration of surfactant (% w/w).
Y1 =drug release (%).
Y2 = disintegration time (s).

EVALUATION PARAMETERS OF PREPARED ORAL DISSOLVING FILMS:

Folding endurance:

Folding endurance is determined by repeated folding of the oral film at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value.[15]

Thickness:

The thickness of oral film can be measured by the micrometer screw gauge at the different strategic locations. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of the dose in the strip.[16]

Percent elongation:

The percentage elongation break was determined by noting the length just before the break point, the percentage elongation was determined from the below mentioned formula.

Elongation percentage = [(L1-L2)/L2] ×100

Where, L1 is the final length of each strip.

L2 is the initial length of each strip.[17]

Dispersion time:

The six films of 2×2 cm2 put in the disintegration tester (USP) ED-2L at room temperature in tubes in the environment of water until they dispersed and that time had been measured.[18]

Assay/drug content and content uniformity:

A specified area of film (2cm×2cm) was dissolved in 100ml water in volumetric flask and shaken continuously for 10 min. After filtration, 1 ml was withdrawn from the solution and diluted to 10ml with methanol. The absorbance of the solution was taken at 210 nm and concentration was calculated which determined the drug content.[19]

***In-vitro* Drug Release test:**

The in vitro dissolution study of Gabapentin oral film was performed using USP apparatus (model TDT08T, Electrolab, Mumbai, India) fitted with paddle (50 rpm) at 37±0.5^{0}C. Dissolution media were 900ml of 6.8 buffer solution for 20 minutes. At the predetermined time intervals, 10ml samples were withdrawn, filtered through a 0.45μm membrane filter, diluted and assayed at 265 nm using a ShimadzuUV1800 double beam spectroscopy.[20]

***In- vivo* test:**

Select an 18 healthy albino rat (male/female) weighing about 200-250gm.

Group 1: Pure drug is administered by calculating the dosage based on animal weight, the animal dose for the drug is 1.3mg/kg by oral route by preparing a suspension of drug in sodium CMC.

Group 2: Film formulation is given on to mouth mucosa. For the administration of sample (tablet/ film) preparation, 50µl aliquate distilled water was dropped in to the rat oral cavity under light ether anesthesia, then to halves (1cm×0.5cm) of the film preparation were applied to the buccal cavity bilaterally. Blood specimen were taken (every 0.5ml) in a centrifuge plastic capillary tube by the intraorbital route at 0, 30 min, 1hr, 2 hr, 4hr, 6hr, 12hr. after drug administration. Blood was subjected to centrifugation at 10000 rpm for 15 min. then plasma was taken in polyethylene tube. To the plasma of 100µl, 100µl Acetonitrile is added and mixed by vortexing for 15 min then centrifuged at 15000 rpm for 30 min and the supernant was injected into HPLC.

Group 3: Marketed formulation is given on to mouth mucosa.[21]

Table 3: Chromatographic conditions

Column	C18
Mobile Phase Acetonitrile: ethanol	(30:70)
Flow rate	1.0ml/min
Injection volume	20µl
Retention time	3.860
Temperature	Ambient

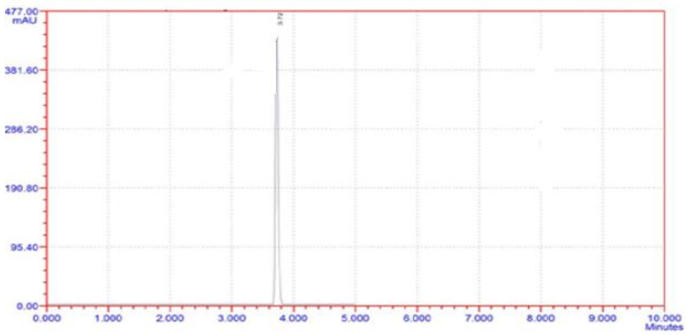


Fig. No.2: Standard chromatogram of Gabapentin.

DETERMINATION OF EVALUATION PARAMETERS:

Code	Thickness(µm)	Weight variations (mg)	Tensile strength (kg/mm^2)	Surface pH	Percent elongation
FDF1	0.9±0.00	90±.01	0.9920±.005	6.760.05	7.67±0.00
FDF2	0.6±0.00	91±.00	0.991±.006	6.00±0.02	3.12±0.02
FDF3	0.7±0.01	92±.02	0.996±.002	6.92±0.02	4.23±0.01
FDF4	0.8±.03	90±.03	0.991±.001	6.64±0.02	2.12±0.03
FDF5	0.8±0.1	89±.00	0.990±.003	6.81±0.01	2.63±0.01
FDF6	0.6±0.2	91±.03	0.996±.000	6.77±0.1	2.79±0.02
FDF7	0.5±0.1	90±.00	0.889±.001	6.68±0.03	5.86±0.00
FDF8	0.9±.00	90±.00	0.990±.002	6.72±0.05	6.10±0.02
FDF9	0.9±.02	91±.04	0.889±.003	6.78±0.01	10.0±0.01
FDF10	0.8±0.00	91±.02	0.990±.001	6.75±0.00	8.86±0.03
FDF11	0.7±0.02	90±.00	0.995±.002	6.92±0.02	7.59±0.02
FDF12	0.7±0.00	90±.01	0.991±.001	6.77±0.1	7.86±0.00
FDF13	0.6±0.01	90±.02	0.996±.007	6.09±0.02	5.11±0.03
FDF14	0.6±0.01	90±.01	0.995±.001	6.72±0.05	4.59±0.01
FDF15	0.4±0.04	90±.01	0.992±.003	7.01±0.4	10.0±0.00
FDF17	0.5±0.02	90±.02	0.997±.000	7.26±0.1	9.1±0.02

Folding endurance(count)	Dis. Time(sec)	Drug content (%)
109±9.2	90±2	87.2±0.4
115±6.02	120±4	82.41±0.2
115±2.02	120±3	82.41±0.1
120±7.23	75±2	106±0.6
140±10.25	80±2	89±0.3
115±9.53	89±2	109±0.6
144±2.0	120±3	82.41±0.5
138±10.08	62±4	118.4±0.2
991±1.50	69±2	92±1.3
115±14.02	120±2	82.41±1.2
115±11.01	120±2	82.41±0.9
118±9.11	85±2	103±0.3
119±8.28	119±1	96±0.9
134±7.62	95±3	74±1.0
100±10.32	90±2	88±0.2
139±9.00	75±4	79±1.3
152±8.64	65±1	67.11±1.1

Table No.4: Evaluation of all parameter including in film.

RESULTS AND DISCUSSION:

Preparation of film formulations:

All the film formulations containing HPMC-15 polymer with propylene glycol as plasticizer were readily prepared by solvent casting. A solvent mixture of water with citric acid, tween 80 as a surfactant and other excipients was required to keep in solution.

Evaluation of Prepared Films:

Surface pH:

An acidic or alkaline pH of administered dosage forms can irritate the buccal mucosa. The measured surface pH was found to be close to neutral in all the formulations which means that they have less potential to irritate the buccal mucosa and therefore they should be fairly comfortable.

Pre-Formulation Study:

A. Melting Point:

Melting point of Gabapentin by capillary method was found to be 162-166^{0}C.

B. Solubility:

The solubility of Gabapentin was checked in different solvents & was found to be Soluble in methanol, ethanol and 0.1N HCl.

Analytical methods for the estimation of gabapentin: -

Reagents: - Gabapentin, 0.1N HCl.

Preparation of standard stock solution of GBP in 0.1N HCl: -

Accurately weighed 500mg of GBP was dissolved in sufficient amount of 0.1N HCl in a 50 ml volumetric flask and diluted to volume with 0.1N HCl. From the above solution, samples of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, and 4 ml was withdrawn in 1000 ml volumetric flasks and diluted to volume with 0.1N HCl so as to obtain standard solutions of concentrations 5, 10, 15, 20, 25, 30, 35 and 40 µg/ml respectively. The absorbance of standard solution was determined at 210 nm.

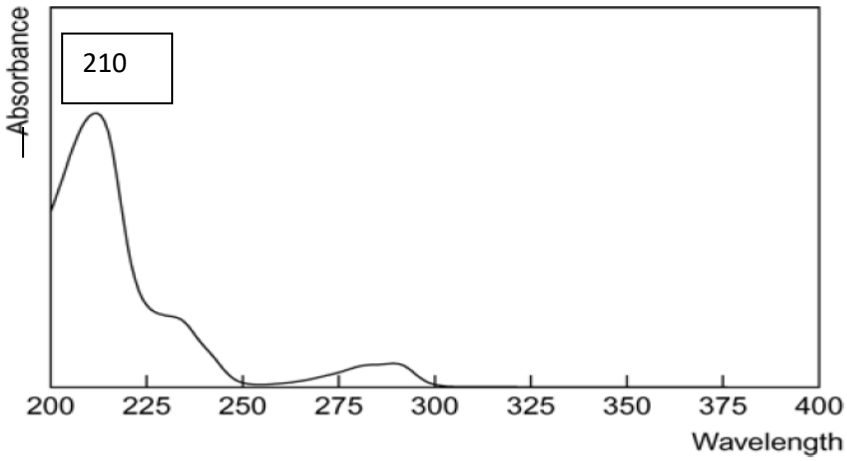


Fig.No.3: UV scans for Gabapentin at 210 nm in 0.1N HCl.

Sr. No	Conc.(µg/ml)	Absorbance.
1	5	0.151
2	10	0.280
3	15	0.441
4	20	0.567
5	25	0.724
6	30	0.821
7	35	0.978
8	40	1.062

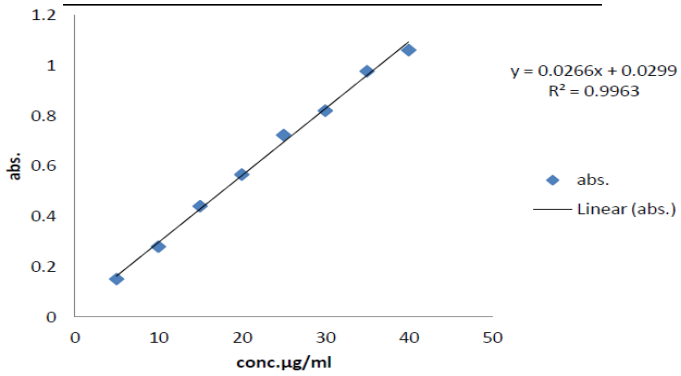


Fig.No:4. Standard calibration curve of Gabapentin 0.1 N HCl

Drug polymer interaction studies by FT-IR spectroscopy: -

1. FT-IR Spectra of Gabapentin.

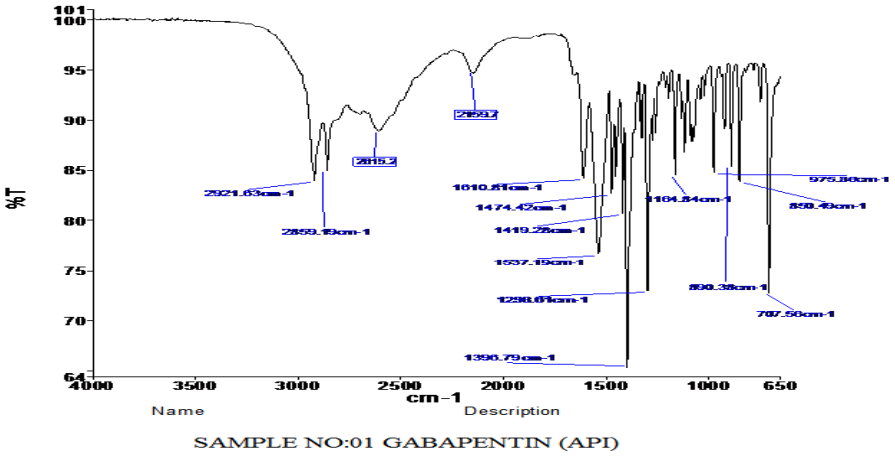


Fig. No.6. FT-IR graph of Gabapentin (API)

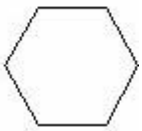
PEAK	FUNCTIONAL GROUPS
1650-1580	-NH
1020-1220	-CN
1300-1400	-COOH
2870-2845	-CH
1440-1395	-OH
1610-1550	-CO
2580-3040	

Table No.5: Data of FT-IR spectra of Gabapentin.

DSC graph of Gabapentin:

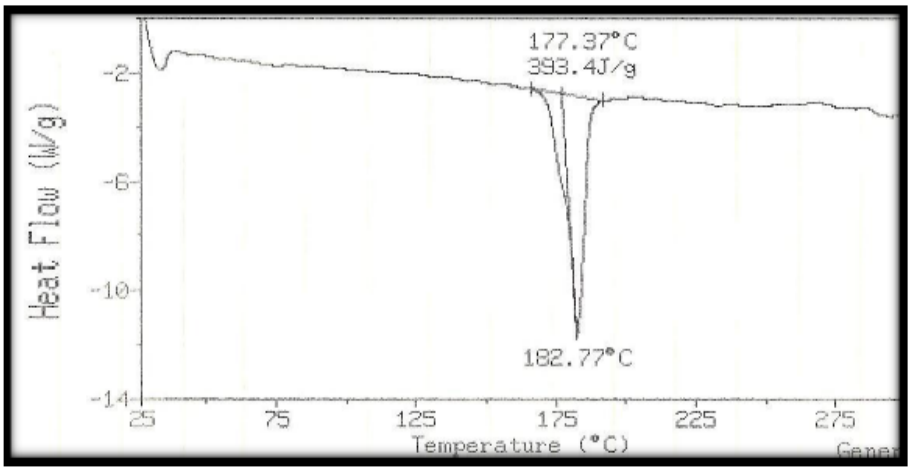


Fig. No.6: Diagram of DSC of gabapentin.

Stability studies:

Stability study was carried out for 30 days in aluminum packaging and kept in humidity chamber maintained at 40 ± 2 °C / 75 ± 5 %RH. At the end of studies, samples were analyzed for the characterization of drug content and other parameters.[22]

Sr. no	study	Storage condition
1.	General case	$30^0C + 2^0C$
2.	Refrigerator	$8^0C + 2^0C$

DoE:

In present investigation, 17- run, 3-factor, 3- levels Box-Behnken design was utilized for creating second order polynomial models and analyzing quadratics response. This design can be used to assess main effects, interaction effects and quadratic effects of factors on dependent variables to optimize the formulation. The quadratic model generated by design was (23-26).

Table.No.6: Coded full factorial Box-Behken design for the three independent variables:

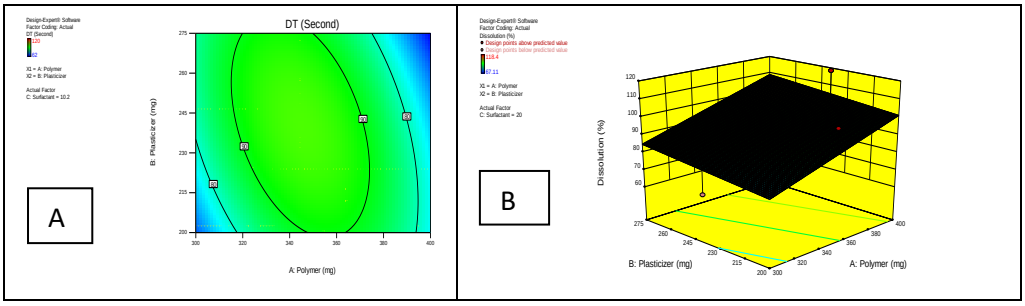
Sr.No	Batch	Independent variable			Observed Value Dependent variables	
		X1	X2	X3	Y1	Y2
1	FDF1	+1	-1	0	87.2	90
2	FDF2	0	0	0	82.41	120
3	FDF3	0	0	0	82.41	120
4	FDF4	+1	0	-1	106	75
5	FDF5	0	+1	-1	89	80
6	FDF6	+1	+1	0	109.6	89
7	FDF7	0	0	0	82.41	120
8	FDF8	+1	0	+1	118.4	62
9	FDF9	0	+1	+1	92	69
10	FDF10	0	0	0	82.41	120
11	FDF11	0	0	0	82.41	120
12	FDF12	0	-1	+1	103	85
13	FDF13	-1	+1	0	96	119
14	FDF14	0	-1	-1	74	95
15	FDF15	-1	-1	0	88	90
16	FDF16	-1	0	-1	79	75
17	FDF17	-1	0	+1	67.11	65

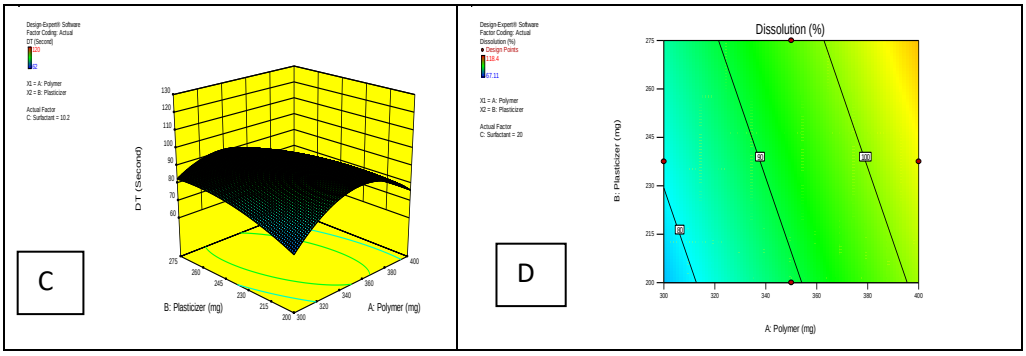
Data analysis:

The model parameters obtained from the analysis of varience (ANOVA) for the responses. These parameters were used to construct the models that describe the effect of the independent variables on the responses.

Final equation in terms of coded factors:

DT = +120.00 - 4.12 * A - 0.37 * B-5.50 * C - 7.50 * AB-0.75 * - 0.2*BC-18.00*A^2 - 5.00*B^2 - 32.75* C^2





Disintegration time:

A. Counter plot showing combined effect of polymer and plasticizer when surfactant kept at low level i.e. 10.2 mg.
B. 3D response surface showing combined effect of polymer and plasticizer when surfactant kept at level 19.59 mg

% Drug release:

C. Counter plot showing combined effect of polymer and plasticizer when surfactant kept at level 15 mg.
D. 3D Response surface showing combined effect of polymer and plasticizer when surfactant kept at higher level 15mg.

Cumulative percentage graph of 1-17 batches.

Table No.7: *In-vitro* dissolution study of F1-F17 batches:

Time(MIN)	Cumulative Percentage Drug Release						
	F1	F2	F3	F4	F5	F6	F7
1	7.731	6.917	16.917	35.804	22.784	23.190	19.004
2	36.063	47.020	49.20	10.552	23.950	32.291	25.690
3	47.835	51.428	61.428	40.158	45.963	47.133	69.245
4	57.925	77.901	69.09	54.059	49.502	69.668	75.524
5	73.589	81.196	88.50	72.856	77.223	92.480	82.037

Time(MIN)	Cumulative Percentage Drug Release					
	F8	**F9**	**F10**	**F11**	**F12**	**F13**
1	24.004	8.542	24.816	47.192	13.424	28.477
2	37.243	23.880	36.628	61.784	49.267	36.310
3	73.468	49.890	60.604	39.381	61.065	67.167
4	76.969	56.807	52.793	136.180	53.267	72.605
5	88.879	85.461	58.488	88.486	97.219	73.717

Time(min)	Cumulative Percentage Drug Release			
	F14	**F15**	**F16**	**F17**
1.	30.107	76.484	92.212	21.012
2.	78.328	33.875	82.372	11.499
3.	87.034	30.444	43.519	23.489
4.	90.696	80.566	94.821	49.782
5.	93.218	95.714	85.139	75.074

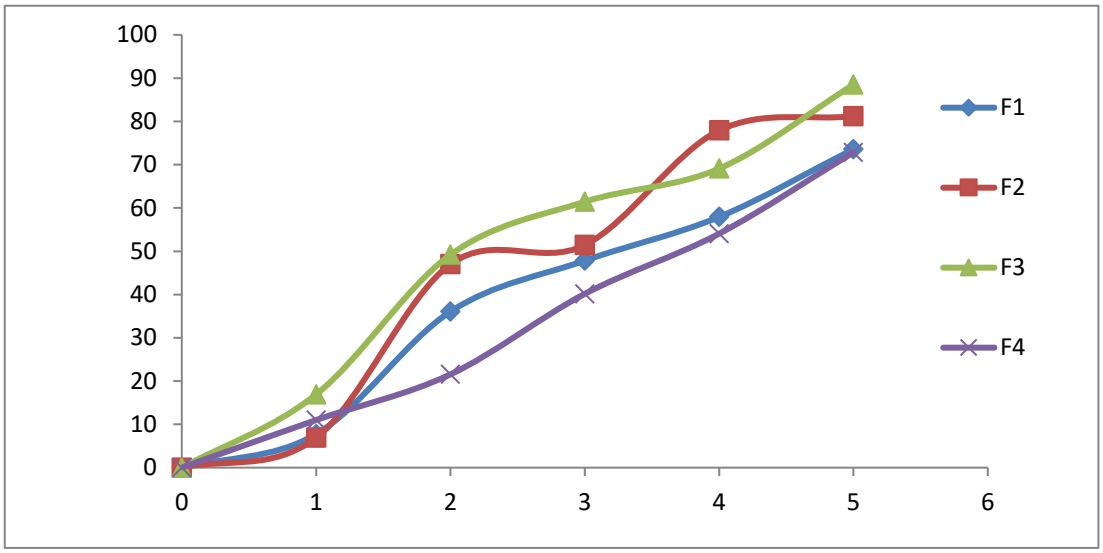


Fig. No.07: *In-vitro* drug release data of formulations (F1 to F4)

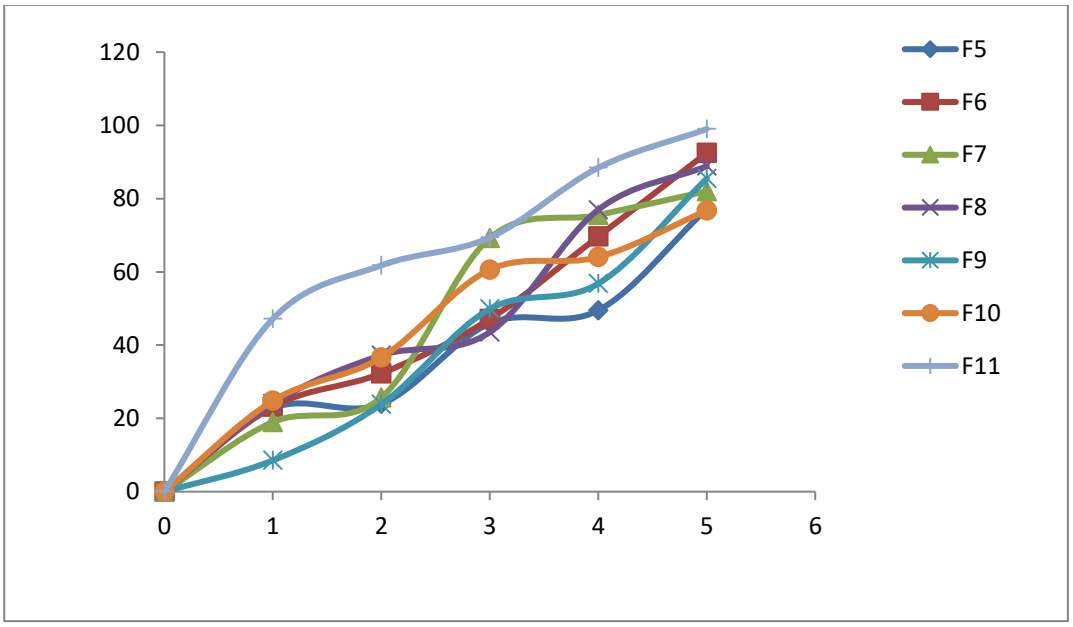


Fig. No.08: *In-vitro* drug release data of formulations (F5 to F11)

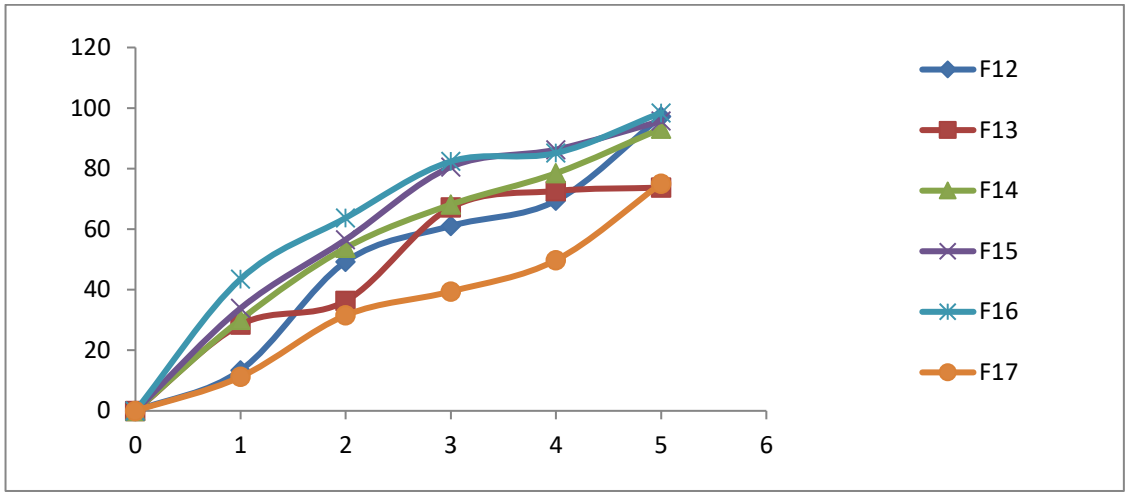


Fig. No.09: *In-vitro* drug release data of formulations (F12 to F17)

Pharmacokinetic Data:

Table No.08 Plasma levels of gabapentin film and pure drug at different time intervals (Mean ± SD, n = 3).

Time(min)	Gabapentin content(µg/m)	
	film	Pure drug
0	0	0
10	780	760
20	812	789
40	609	537
80	424	288
160	98	36
320	41	17

Table 09: Comparison of pharmacokinetic parameters of gabapentin between the film and reference (oral solution of the pure drug) in rats (mean ± SD, n = 3).

parameter	Film(sample)	Pure drug(reference)
AUC_{0-t} (ng.h/ml)	1986.099±49.18	1905.366±53.9
AUC_{∞}(ng.h/ml)	2043±59.32	192433±53.18
C_{max} (µg/ml)	862	793
T_{max}(minute)	45	45
Kel(h^{-1})	0.841±0.771	0.732±0.901
$t_{1/2}$(h)	2.590±0.229	2.599±0.413

Bioavailability Parameters

The mean gabapentin plasma concentrations - time profiles for the prepared gabapentin film and the pure drug gabapentin are shown in Table No.08 The bioavailability parameters for the both test film and reference standard are summarized in Table No.09 The statistical comparison of C_{max}, T_{max}, $AUC_{0-\infty}$ and AUC_{0-t} indicated no significant difference between the two treatments, also no significant difference for the period effect was observed in this study based on the statistical inferences it was concluded that the two formulations exhibited comparable plasma level time profiles.

CONCLUSION:

In the present investigation an attempt was made to develop mouth dissolving films of Gabapentin to achieve fast disintegration and dissolution characteristics with improved bioavailability by oral

route. The drug and excipients were characterized as per USP 2014. Drug and excipients studies were conducted using UV, FT-IR & DSC. A 3-factor, 3-level design was observed to be the most suitable and appropriate for exploring quadratic response. Gabapentin oral film was evaluated for folding endurance, thickness, weight variation test, surface pH, content uniformity, disintegration test, and in-vitro dissolution and in-vivo study. The stability studies of the films were performed for optimized batch as per ICH guideline. As per DOE 17 different formulation trials were carried out. The optimized batch showed a disintegration time of 60 seconds and maximum % drug release was within 120 seconds.

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