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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 levels). 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 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.

KEYWORDS: Oral film of gabapentin was optimization, 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 other 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. Neuropathic pains 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 breastfeeding. 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 convience of easily swallowable dosage form. In case of allergic condion 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 onset of action, increased bioavailability and good stability make this film popular as a dosage form of drug.[5]

MATERIALS AND METHODS

Gabapentin was purchased from Wockhardt pvt. Ltd, Aurangabad. Hydroxyl propyl methyl cellulose E15, citric acid was procured from Research-lab fine chem. industries, Mumbai. Propylene glycol and menthol were purchased from Meher chemie, Ratnakar Apt. Mumbai. All other reagents were of analytical grade.

METHODS

Preparation of gabapentin oral fast dissolving film by solvent casting method

Films were prepared by using different grades of hydroxyl propyl methyl cellulose by casting method (Lutfulkabir AK, 2009). HPMC E15 was used to formulate film and E15 was selected due to the less brittleness of the film.[6] 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.[7] 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.[8] 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. Film cut into 2×2 cm^2 size and preserved in aluminum foil and stored.[9]

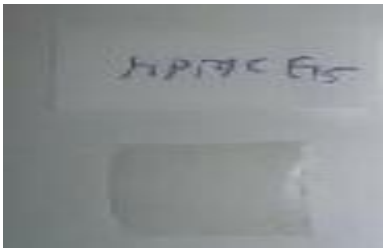

Fig. No.2: Photography of film of Gabapentin.

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.[10] 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.[11]

Table 1: 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

EVALUATION PARAMETERS OF PREPARED ORAL DISSOLVING FILMS

Weight variation of the film

2 x 2 cm^2 film was cut at three different places in the casted film. The weight of each film strip was taken and the weight variation was calculated.

pH studies

The pH was determined by dissolving a film in 2 ml of distilled water and then the pH of the obtained solution was measured by pH meter.[12]

Thickness of the film

The thickness of the film was measured using digital vernier caliper with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different spots of the film and average was taken and SD was calculated.

Folding endurance

The folding endurance is expressed as the number of folds required to break the specimen or develop visible cracks. This gives an indication of brittleness of the film. A small strip of 2×2

square cm was subjected to this test by folding the film at the same plane repeatedly several times until a visible crack was observed.[13]

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= final length of each strip.

L2= initial length of each strip.[14]

Dispersion time

The six film 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.[15]

Drug Content uniformity

Drug content uniformity of all six batches was determined by UV-Spectrophotometery method. For this, each strip at three different places equivalent to 2 mg of drug was cut and dissolved in 50ml of 6.8Ph phosphate buffer solution with continuous stirring. This solution was filtered using Whattmann filter paper, and the filtrate was diluted to 100ml with the same buffer in a volumetric flask. This solution was analyzed by U.V Spectrophotometer and the absorbance was recorded at 210 nm. Drug content was calculated by using calibration curve of drug.[16]

In vitro Dissolution studies

Dissolution study was carried out using USP type I (basket apparatus) with 90 ml of 6.8 pH Phosphate buffer as dissolution medium maintained at 37 ±0.50 C. Medium was stirred at 100 rpm for a period of 30 minutes. Samples were withdrawn at every 5 min interval up to 20 min, replacing the same amount with the fresh medium. Samples were suitable diluted with 6.8pH and analyzed for drug content at 210 nm. Cumulative percent drug release of gabapentin.[17]

***In-Vitro* Drug Release test**

The in vitro dissolution study of gabapentin oral film was performed using USP apparatus (model TDT08T, Electro lab, 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.[18]

***In- vivo* test**

Application to be submitted to the CPCSEA, New Delhi after approval of Institutional Animal Ethics Committee (IAEC).

Part A

1. Name and address of establishment: Channabasweshwar Pharmacy College, Kava Road, Latur. 413512.
2. Registration number: CBPCL/IAEC/2015-2016/07.
3. Name, address and registration number of breeder from which animals acquired (or to be acquired) for experiments mentioned in parts B & C:
   Wokhard Research Centre D-4, MIDC, Chikhalthana, Aurangabad.13/PO/RcBi/SL/99/CPCSEA (10.3.1993).
4. Place where the animals was kept (or proposed to be kept): Channabasweshwar Pharmacy College Animal House, Latur.

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.[19]

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 intra orbital 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.[20, 21]

RESULTS AND DISCUSSION

Pre-Formulation Study

Melting point of gabapentin by capillary method was found to be 162-166^{0}C. The solubility of gabapentin was checked in different solvents & was found to be Soluble in methanol, ethanol and 0.1N HCl.

Determination of λmax

λmax of gabapentin was found to be 210 nm as it shows maximum absorbance in this wavelength.

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.

Physical appearance and surface texture

The observation by visual inspection of films and by feel or touch, suggests that the films are having smooth surface.

Thickness of films

The thicknesses of the films were in the range of to 0.051±0.007mm to 0.037±0.002mm. The results of average thickness of all films**.**

Weight uniformity test

The weights of the films were found to be in the range of 10+0.24mg to 12±0.63mg. The results of average weight of all films.

Folding endurance

Folding endurance of the films was found to be in the range of 13.60±1.31 to 38.62±1.52.The results of average folding endurance of all films were carried out.

Surface pH

The surface pH of all the films were found to be near to be of neutral pH i.e 7.

Drug content uniformity test

The drug content uniformity was performed by taking three films in each formulation trial and the average drug content was calculated. The results were found to be in the range of 97.56±0.31% to 98.90±0.26%.

Dispersion test

The disintegration times of the prepared films were in the range of 5.33±0.57 to 8±1.73sec.

***In-Vitro* dissolution studies**

Gabapentin oral film formulation dissolution study was conducted in 6.8pH phosphate buffer solution as this was similar to the pH of simulated salivary fluid. A modified dissolution methodology was followed to simulate the conditions of the oral cavity. The dissolution volume consists of 900ml of 6.8pH phosphate buffer solution at 37±0.5˚C, which was rotated at 100rpm. Gabapentin from each formulation was carried out in 6.8 pH phosphate buffer solution for 20min. The dissolution study was conducted for 20 min. The drug release was found to be in the range of 80±0.2 to 106±0.01% and the % drug release was maximum. The formulation F6 showed higher drug release of 90±0.01%.

Stability studies

The formulation of F6 was evaluated for stability studies which was stored at 40˚C / 75% RH for 3 months and evaluated for their physical appearance, drug content and *in-Vitro* disintegration time and % drug release at the end of 1st and 3rd month.

DoE

In present investigation, 06- 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.

Table 8: 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	50	90

Table 8: 3^3 Factorial designs with upper, middle, and lower limits of all factors.

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.

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 & excipients were characterized as per USP 2014. 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, & *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 6 different formulation trials were carried out. The optimized batch showed a disintegration time of 50 seconds & maximum % drug release was within 90 seconds.

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