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Formulation Development and Evaluation of Mouth Dissolving Strips of Perampanel

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ABSTRACT:

The research titled "Formulation development and evaluation of mouth dissolving strips of Perampanel" aims to optimize a novel drug delivery system for the antiepileptic drug Perampanel. This study investigates mouth-dissolving strips as an alternative to traditional oral dosage forms, particularly for patients facing swallowing difficulties. The formulation process involves careful selection of film-forming agents and plasticizers. Utilizing a 32 Full Factorial Design, the optimized batch demonstrates favorable mechanical properties and drug release characteristics. Noteworthy statistical outcomes include a disintegration time of 30.1 ± 0.097 seconds and a 95.12 ± 0.26% cumulative drug release at 5 minutes. The mechanical strength, assessed through folding endurance, is found to be 275 ± 2.045. The solubility study reveals Perampanel's high solubility in N-methyl pyrrolidone, shaping the formulation approach. FTIR analysis confirms drug purity and compatibility with chosen excipients. Spectrophotometric analysis establishes UV absorption maxima, enabling accurate drug quantification through a calibration curve. DSC-based drug-excipient compatibility study ensures formulation stability and effectiveness. In conclusion, this research successfully develops and evaluates Perampanel-loaded mouth dissolving strips, demonstrating promising drug delivery properties. The study highlights the potential of this innovative delivery system to enhance patient adherence and therapeutic outcomes. The findings contribute valuable insights into pharmaceutical advancements, setting the stage for further research in mouth dissolving strips for Perampanel and analogous drugs.

KEYWORDS: Perampanel, mouth dissolving strips, drug delivery, formulation development, optimization, disintegration time, drug release, solubility study, compatibility study, patient compliance.

INTRODUCTION [1-6]

In the realm of pharmaceutical research and development, the pursuit of innovative drug delivery systems has been driven by the aim to enhance patient compliance, improve therapeutic outcomes, and elevate the overall quality of healthcare. One such paradigm-shifting innovation is the formulation and evaluation of mouth-dissolving strips, a novel dosage form that transcends traditional administration routes. The development of these strips stands as a testament to the incessant quest for patient-centric solutions that redefine the boundaries of pharmaceutical science.

The conventional administration of drugs through oral tablets and capsules has long been the cornerstone of pharmaceutical therapy. However, this route presents challenges, particularly for certain patient populations such as pediatrics, geriatrics, and those with dysphagia. In response to these challenges, the field of drug delivery has witnessed a paradigm shift, emphasizing patient comfort and convenience without compromising therapeutic efficacy. Within this context, mouth dissolving

strips have emerged as a promising alternative that offers several distinct advantages over conventional oral dosage forms.

Mouth-dissolving strips, also known as oral thin films, offer a unique proposition under their rapid disintegration and subsequent dissolution upon contact with saliva. This characteristic makes them particularly suitable for patients who face difficulties in swallowing conventional tablets and capsules. Moreover, the enhanced surface area of these strips allows for efficient drug absorption through the oral mucosa, thereby potentially circumventing first-pass metabolism and enabling rapid onset of action.

The appeal of mouth-dissolving strips extends beyond their patient-friendly attributes. These strips often exhibit improved bioavailability, reduced side effects, and the potential for controlled drug release profiles. Additionally, their discreet and portable nature lends itself well to patient self-administration, enabling enhanced medication adherence and flexibility in dosing.

The formulation and evaluation of mouth dissolving strips is a multifaceted endeavor that requires a comprehensive understanding of pharmaceutical sciences, materials engineering, and patient preferences. The intricate interplay between excipients, active pharmaceutical ingredients (APIs), and manufacturing techniques underscores the complexity of this field. This pursuit entails not only optimizing the strip's physical and chemical properties but also ensuring its efficacy, stability, and reproducibility.

The application of mouth dissolving strips extends beyond improving patient compliance. It finds resonance in various therapeutic areas, including but not limited to pain management, cardiovascular disorders, neurological conditions, and allergy relief. These strips have demonstrated their potential to revolutionize the pharmaceutical landscape by addressing unmet clinical needs and providing novel delivery solutions.

This article delves into the realm of "Formulation Development and Evaluation of Mouth Dissolving Strips of Perampanel," exploring the nuances of this innovative dosage form. It encompasses an in-depth exploration of the formulation strategies employed to ensure optimal drug delivery, the evaluation methodologies to assess strip performance, and the potential implications for patient care and therapeutic outcomes. By delving into the intricacies of this evolving field, we aim to shed light on the scientific advancements that are reshaping the pharmaceutical industry.

In the subsequent sections, we will embark on a journey through the various stages of the development and evaluation process. From the selection of excipients and active ingredients to the characterization of disintegration time, drug release profiles, and patient acceptance, this article aims to provide a comprehensive overview of the multifaceted landscape of mouth dissolving strips.

In conclusion, the formulation and evaluation of mouth-dissolving strips represent a convergence of scientific innovation, patient-centric design, and enhanced therapeutic efficacy. The journey from conceptualization to realization has underscored the importance of interdisciplinary collaboration and an unwavering commitment to improving patient outcomes. As we delve into the intricacies of "Formulation Development and Evaluation of Mouth Dissolving Strips of Perampanel," we embark on a voyage through the dynamic landscape of pharmaceutical science, one that holds the promise of transforming the way medicines are administered and experienced by patients worldwide.

MATERIALS AND METHODS [7-14]

The research methodology employed in the study titled "Formulation development and evaluation of mouth dissolving strips of Perampanel" was a comprehensive and systematic approach that encompassed various stages, from pre-formulation studies to optimization and validation. This section provides an in-depth overview of the methodology used in the research.

1. Pre-formulation Studies:

The research commenced with a thorough investigation of Perampanel, the active pharmaceutical ingredient (API). This involved conducting pre-formulation studies to characterize the physical and chemical properties of the API. The melting point analysis was carried out to determine the range of temperature at which the solid API transitions to a liquid state. The observed melting point was compared with the reference value to ensure the purity of the API. Additionally, solubility studies were conducted using different solvents to understand the drug's solubility profile. This preliminary data provided insights into the drug's behavior in various solvents and facilitated the subsequent formulation development.

2. Formulation Development:

The formulation development phase aimed to design mouth dissolving strips that would effectively deliver Perampanel. A 32 full factorial design was employed,

which is a powerful experimental design technique. It allowed for the systematic exploration of the effects of different factors, such as the concentration of excipients like binders, disintegrants, and plasticizers, on critical parameters like disintegration time, drug release, and folding endurance. The levels of the factors were selected based on initial trials and literature review, ensuring a rational approach to formulation development.

3. Drug-Excipient Compatibility Study:

To ensure the stability and compatibility of the formulated mouth-dissolving strips, a drug-excipient compatibility study was conducted using Differential Scanning Calorimetry (DSC). This technique involved subjecting the formulated strips to controlled temperature changes while monitoring heat flow. Any significant interactions between the drug and excipients would be reflected in the DSC thermograms. This step was crucial to ensure that the formulation components did not adversely affect the drug's chemical integrity and efficacy.

4. Evaluation Techniques:

The developed mouth-dissolving strips underwent a rigorous evaluation process to assess their performance. Disintegration time, a critical parameter for orally disintegrating dosage forms, was determined using standardized methods. Drug release studies involved measuring the percentage of drug released from the strips over time using a dissolution apparatus. Folding endurance, which indicates the flexibility and robustness of the strips, was also assessed. Additionally, Fourier Transform Infrared (FTIR) analysis was conducted to study any potential interactions between the drug and excipients on a molecular level.

5. Statistical Analysis and Optimization:

Statistical tools played a pivotal role in the research methodology. Design Expert software facilitated the design of experiments, regression analysis, and the generation of polynomial equations. Analysis of Variance (ANOVA) was employed to determine the significance of factors and their interactions on the responses. The optimization process utilized overlay plots to visualize the combinations of factors that resulted in desired outcomes. This data-driven approach enhanced the understanding of the formulation's behavior and aided in identifying the optimal formulation.

6. Validation and Comparison:

A checkpoint batch was selected based on the overlay plot results, and its performance was evaluated. This validation step ensured the reliability and reproducibility of the developed formulation. Furthermore, the experimental results were compared with the predicted values obtained from the statistical models. This comparison validated the accuracy of the models in predicting the responses and demonstrated the efficacy of the methodology.

Conclusion:

In conclusion, the research methodology followed a systematic and scientific approach to develop and evaluate mouth-dissolving strips containing Perampanel. The incorporation of pre-formulation studies, experimental design, statistical analysis, and thorough evaluation techniques contributed to a comprehensive understanding of the formulation's characteristics. This methodology not only advanced the field of formulation development but also demonstrated the importance of data-driven approaches in pharmaceutical research. The findings of this study could potentially pave the way for the development of innovative drug delivery systems with enhanced efficacy and patient compliance.

RESULTS AND DISCUSSIONS [15-20]

CHARACTERIZATION AND PRE-FORMULATION STUDY

Melting Point Determination

Table 1 Melting point analysis of Perampanel

Reference Melting Point Range	Observed Melting Point
175-176 ˚C	174˚C

Solubility Study

Table 2 Solubility study of Perampanel

Sr No.	Solvent	Solubility*	Type of solubility
1	Water	10034	Very slightly Soluble
2	Methanol	156	Soluble
3	Ethanol	140	Slightly Soluble
4	N-methyl pyrrolidone	04	Freely soluble
5	Acetonitrile	40	Sparingly Soluble
6	Phosphate Buffer 6.8	36	Sparingly Soluble

*Parts of solvents required for part of solute.

Solubility of Perampanel was found in each solvent and it is highly soluble in the solvent N-methyl pyrrolidone.

FTIR Study

FTIR study of Perampanel was done to identify functional groups for the characterization.

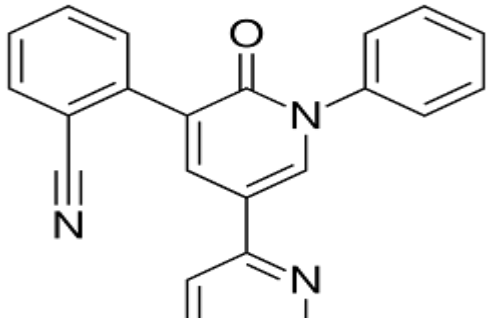

Figure 1 Chemical Structure of Perampanel

Table 3 Interpretation of FTIR spectrum of Perampanel

Sr. No.	Functional group	Observed frequencies (Cm^{-1})	Reported frequencies (Cm^{-1})
1	NH	3424.58	3300-3500
2	Aromatic C-H	3072.27	2950-3100
3	C=N	2218.90	2200-2250
4	C=O	1662.63	1650-1750
5	C≡N	1567.5	1500-1600
6	C=C	1435.03	1400-1500
7	NH	3424.58	3300-3500

Major peaks of Perampanel were found to be stretching of C≡N, C=O and C=N group.

PRELIMINARY STUDY

Selection of Film Forming Agent and Plasticizer

Preliminary batches were formulated using different film-forming agent such as Pullulan, sodium alginate, HPMC E15, HPMC E5 and a different plasticizer such as and PEG 400.

Table 4 Evaluation of preliminary batches (PT1 to PT7)

Parameters	PT1	PT2	PT3	PT4	PT5	PT6	PT7
Size (mm)	20x20	20x20	20x20	20x20	20x20	20x20	20x20
Thickness (mm)	0.125	0.123	0.126	-	0.120	0.128	-
Surface pH	6.5	6.6	6.6	-	6.7	6.8	-
Weight variation (mg)	295	260	345	-	370	290	-
Folding endurance	160	164	257	-	218	185	-
Disintegration time (sec)	**124**	**103**	**97**	**-**	**196**	**211**	**-**

Table 5 Evaluation of preliminary batches (PT8 to PT15)

Parameters	PT8	PT9	PT10	PT11	PT12	PT13	PT14	PT15
Size(mm)	20x20	20x20	20x20	20x20	20x20	20x20	20x20	20x20
Thickness (mm)	-	0.137	-	-	0.128	0.124	0.132	0.118
Surface pH	-	6.8	-	6.9	7.0	6.9	7.0	6.8
Weight variation(mg)	-	267	-	324	356	365	297	310
Folding endurance	-	266	-	260	285	308	256	276
Disintegration time (sec)	**-**	**71**	**-**	**110**	**18**	**81**	**95**	**19**

OPTIMIZATION OF MOUTH DISSOLVING STRIP OF PERAMPANEL USING 3^2 FULL FACTORIAL DESIGN

Evaluation of Factorial Batches

Evaluation of factorial batches F1-F9 is given below.

Table 6 Evaluation of factorial batches

Parameters	F1	F2	F3	F4	F5
Size (mm)	20x20	20x20	20x20	20x20	20x20
Thickness (mm)	0.111 ± 0.002	0.103 ± 0.002	0.108 ± 0.003	0.113 ± 0.002	0.115 ± 0.002
Surface pH	6.8 ± 0.133	6.9 ± 0.098	6.9 ± 0.101	0.285 ±0.05	0.310±0.013
Weight variation (mg)	0.298 ± 0.035	0.310± 0.011	0.321 ± 0.014	7.0 ± 0.123	6.8 ± 0.101
% Drug content	98.3±0.32	98.9±0.17	99.2±0.21	98.7 ± 0.179	99 ± 0.093
Folding endurance	276± 1.414	250 ± 2.327	301 ± 2.244	293 ± 1.624	297 ± 2.039
Disintegration time (sec)	30± 0.489	22 ± 0.198	26 ± 1.010	35 ± 0.097	31 ± 0.748
% CDR at 5 min	91.46± 0.45	94.64± 0.24	88.35 ± 0.25	88.27 ± 0.18	89.57 ± 0.21

Average ± standard deviation (n=3)

Parameters	F6	F7	F8	F9
Size (mm)	20x20	20x20	20x20	20x20
Thickness (mm)	0.117 ± 0.003	0.108± 0.002	0.118 ± 0.002	0.121 ± 0.003
Surface pH	0.325±0.009	6.9 ± 0.195	6.9 ± 0.248	6.9 ± 0.103
Weight variation (mg)	6.8 ± 0.132	0.300 ± 0.004	0.302 ± 0.018	0.294 ± 0.016
% Drug content	99.56 ± 0.80	99.24 ± 0.326	98.92 ± 0.074	99.3 ± 0.141
Folding endurance	270 ± 2.520	282 ± 2.039	260 ± 2.717	255 ± 3.120
Disintegration time (sec)	33 ± 1.019	14 ± 0.549	27 ± 0.982	19± 1.102
% CDR at 5 min	92.14 ± 0.30	95.55 ± 0.14	91.3 ± 0.25	94.28 ± 0.41

Average ± standard deviation (n=3)

In-Vitro Drug Release

In-vitro drug release profiles of the all factorial batches F1-F9 are given in the following table.

Table 7 *In-vitro* drug release of factorial batches

Time (min)	% Cumulative Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	22.12±0.37	23.45±0.69	16.65±0.41	16.5± 0.70	17.45±0.75	21.78±0.21	24.49±0.15	23.87± .45	27.65±0.64
2	49.31±0.62	50.65±0.51	37.12±0.59	37.24±0.78	39.34±0.35	45.22±0.45	49.63±0.65	46.23±0.24	58.44±0.54
3	64.32±0.89	69.65±0.41	56.71±0.30	55.23±0.38	58.43±0.24	65.78±0.75	68.45±0.80	69.46±0.36	71.36±0.44
4	81.56±0.19	85.56±0.33	73.51±0.88	74.78±0.40	76.87±0.25	81.54±0.64	83.35±0.45	81.72±0.21	86.78±0.51
5	91.46±0.21	94.64±0.28	88.35±0.32	88.27±0.29	89.57±0.71	92.14±0.19	95.55±0.20	91.3± 0.15	94.28±0.24

Average ± Standard Deviation (n=3)

Generation of Quadratic Model for 32 Full Factorial Design

Table 8 Quadratic model regression analysis for 32 full factorial design

Y1 – Disintegration Time (sec)	R1= 30.44+4.67*A-3.67*B+2.00*AB-5.67*A^2 -0.6667*B^2
Y2 - % Drug Release (At 5 min)	R2= 90.99-0.8650*A+0.2300*B-2.10*AB
Y3 - Folding Endurance	R3= 276.00+21.00*A+5.00*B

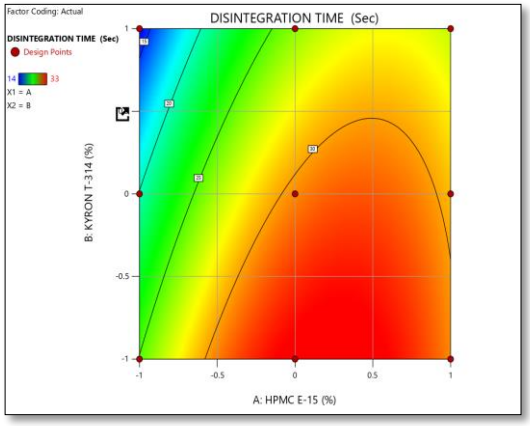

Figure 2 Contour plot of response Y_1

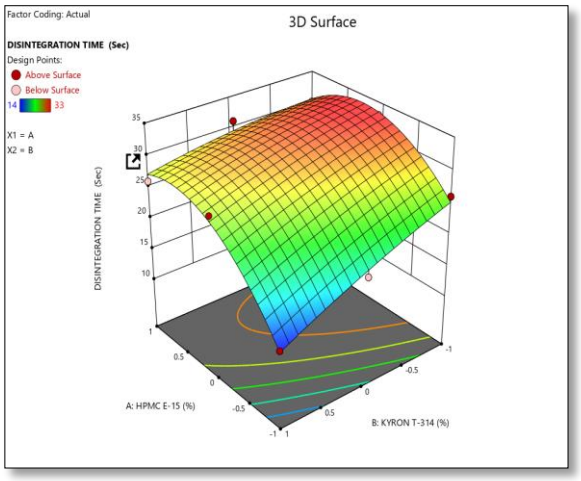

Figure 3 3-D Surface contour plot of response Y_1

As observed from the 3-D surface counter plot and the contour plot, the effectiveness of concentration HPMC E15 (X_1) is more on the response Y_1 (Disintegration time) than that of concentration of PEG- 400 (X_2). As seen in contour plot concentration of HPMC E15 increases, disintegration time increases and concentration of plasticizer increases, disintegration time decreases but if concentration of plasticizer in higher level than disintegration time increases so it is concluded that concentration of plasticizer should be in medium level.

A positive sign of HPMC E15 and negative sign of PEG- 400 indicate the direct and inverse proportionality with response Y_1 respectively.

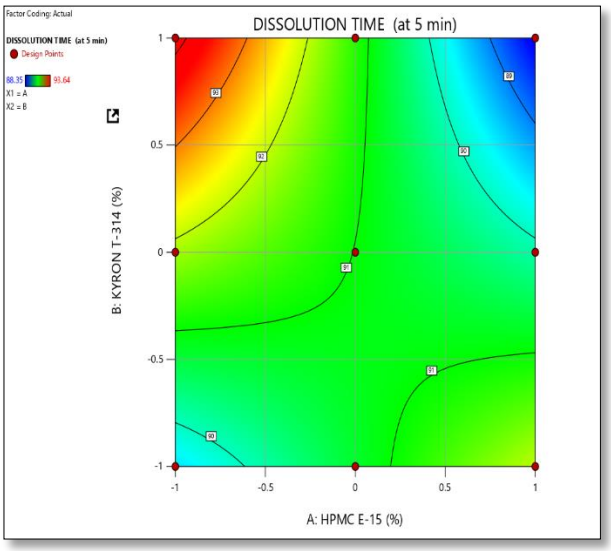

Figure 4 Contour plot of response Y_2

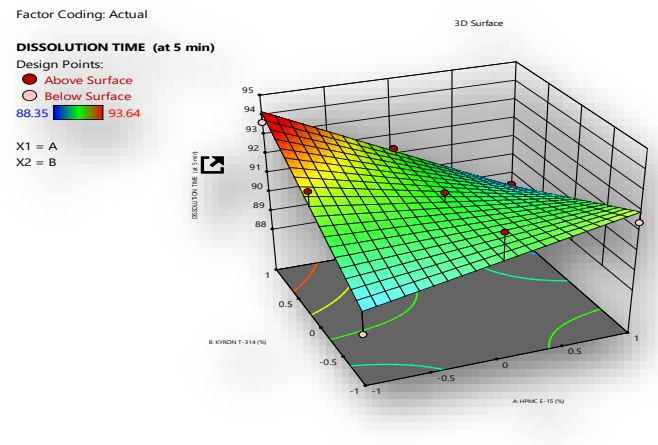

Figure 5 3-D Surface contour plot for response Y_2

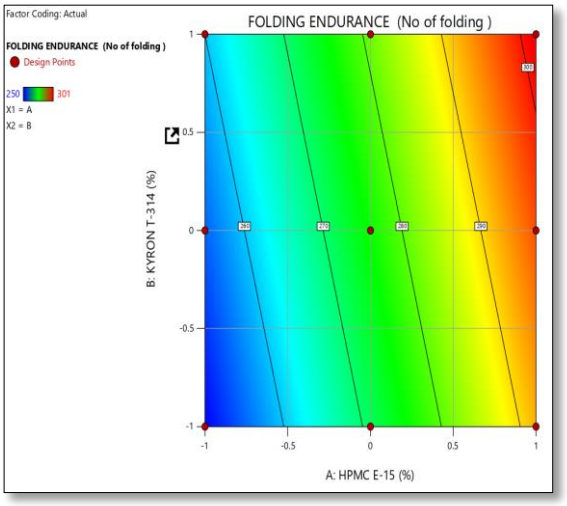

Figure 6 Contour plot of response Y_3

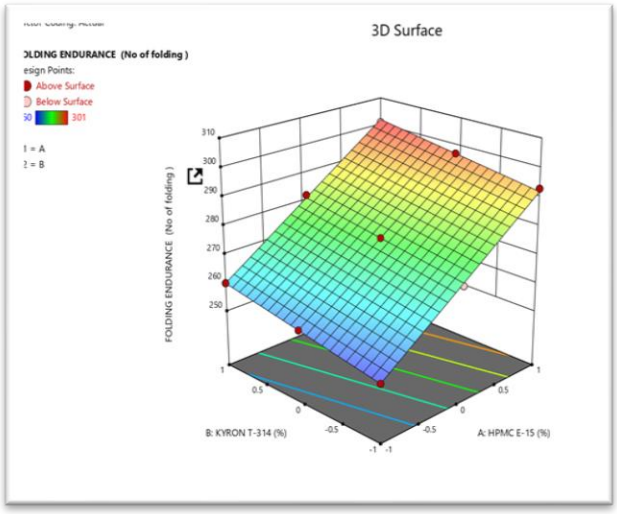

Figure 7 3-D Surface contour plot of response Y_3

Optimization of Formulation by Overlay Plot

The 3^2 Full Factorial Design was applied for the determination of the effects of independent variables on the responses. In this study the effect of independent variables X_1 (concentration of HPMC E15) and X_2 (concentration of PEG- 400) were analyzed and the optimized batch was selected from the overlay plot of these variables with the dependent variables Y_1, Y_2 and Y_3.

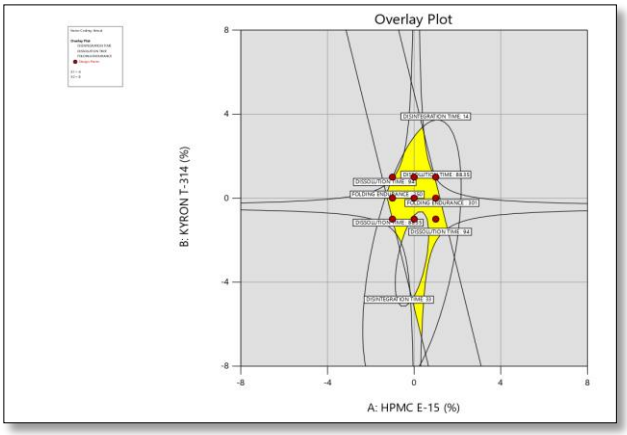

Figure 8 Overlay plot of responses with respect to independent variables

Optimized area was generated by Design Expert 13 using Overlay plot is given in the figure 6.21 any combinations of independent variables in the yellow region will give the desired results on dependent variables. Moreover, Response Y_1 (Disintegration time) was set in the range of, Response Y_2 (drug release) was set in the range of and Response Y_3 (folding endurance) was set in the range of.

Check Point Batch

From the overlay plot the validation batch was selected at X1 = 525 mg and X2 = 140 mg which is very near to optimized batch. Overlay plot with the selected two point

for the validation batch is given below. Checkpoint batch was evaluated for different evaluation parameters.

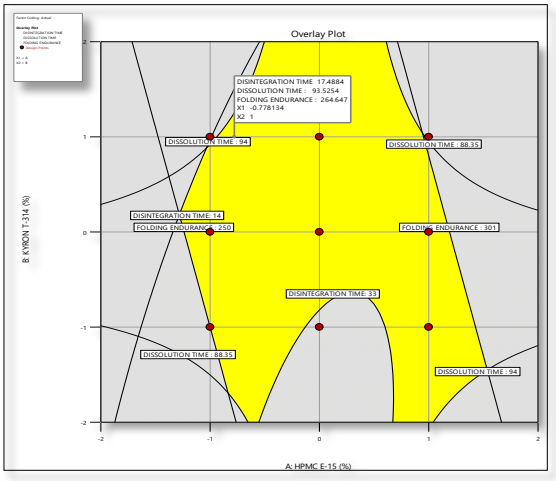

Figure 9 Overlay plot for check point batch

Evaluation of Check Point Batch

Table 9 Evaluation of checkpoint batch

Evaluation	Initial observation
Surface pH	6.9±0.05
% Drug content	98.6 ± 0.548
Folding endurance	275 ± 2.045
Disintegration Time (sec)	30.1 ± 0.097
% CDR at 5 min	91.56 ± 0.26

Table 10 In-vitro drug release of check point batch

Time (min)	% Cumulative Drug Release
	Check point batch (C1)
0	0
1	28.74 ± 0.78
2	59.45 ± 0.45
3	76.65 ± 0.69
4	88.19 ± 0.87
5	95.12 ± 0.26
Average ± Standard Deviation (n=3)	

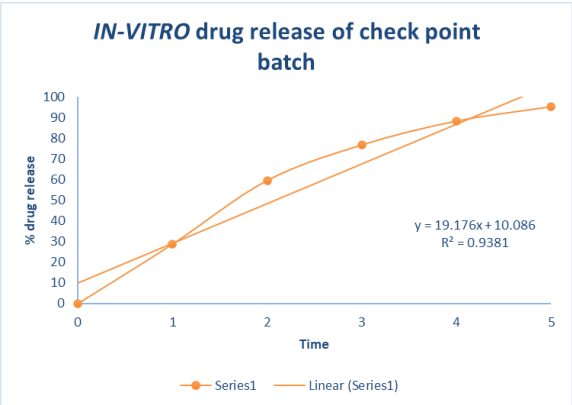

Figure 10 In-vitro drug release of check point batch

Comparison of Experimented and Predicted Values

Table 11 Comparison of experimented and predicted Check Point batch

Analysis	Predicted Mean	Predicted Median	Observed	Std Dev
Disintegration time	19.7144	19.7144	20	1.5396
Dissolution time	92.948	92.948	93	0.994606
Folding endurance	264.16	264.16	264	0.816497

For the result predicted mean was 19.71 (Disintegration Time), 92.94 (Dissolution Time), 264.16 (Folding Endurance). Where the standard observe value were 20, 93, 264 which is considers as good results.

The Experimental values of responses Y1, Y2 and Y2 were found to be very close to the predicted value generated by the Design expert 13 software which indicate the good reproducibility and good prediction ability.

CONCLUSION

The present research work is on the formulation and evaluation of Mouth dissolving strip of Perampanel. Perampanel is also known as anti-epileptic drug, is available in different forms. I.e., Perampanel available tablet dosage form under Fycompa, is anti-epileptic drug which is used to treat partial onset seizures for people older than twelve years. The current formulation of Perampanel is present in form of tablet and suspension. Oral dosage form has forms have low patient compliance. Absorption through the oral route is low it takes time to get action. Therefore, present research was carried out on mouth dissolving strip formulation of Perampanel which increases patient compliance as well as the instant drug action.

The mouth dissolving strip is prepared by solvent casting method which is easy, requires less time, and cost-effective method compared to other oral strip-making methods. A solubility study of Perampanel in various solvents was done. The highest solubility of Perampanel was found in N-methyl pyrrolidone. FTIR study and melting point determination of Perampanel were done to check the purity of the drug and it was found satisfactory which indicates that the drug is pure. Spectrophotometric analysis of Perampanel was done in water for the calibration curve.

Preliminary batches were made by different film-forming agents and plasticizers to find out the excipients giving the best results in terms of disintegration time and folding

endurance. The HPMC E15 was selected as film forming agent and PEG-400 was selected as plasticizer which also act as permeation enhancer. The drug excipient compatibility was checked by DSC, it shows no interaction so there is no drug excipient incompatibility. Two independent factors – concentration of film forming agent (X1) and concentration of plasticizer (X2) were selected for 32 full factorial design and nine batches F1-F9 were formulated and evaluated by three dependent responses – Disintegration time (Y1), % Drug release (Y2) and Folding endurance (Y3). The best result was found in the batch F7 giving faster disintegration in only 14 seconds, folding endurance of 282 ± 1.624 and 95.55 ± 0.20 % cumulative drug release at 5 minutes. So, the F7 batch was considered as optimized batch. Design Expert 13 was used to see the effect of independent variables – concentration of film forming agent (HPMC E15) and concentration of plasticizer (PEG-400) on the dependent variables – Disintegration time, % Drug release and folding endurance in the formulation by quadratic polynomial model.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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