IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

FORMULATION AND EVALUATION OF FLOATING TABLET OF TAPENTADOL HYDROCLORIDE

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Abstract

The study aimed to develop sustained-release floating tablets of Tapentadol HCl utilizing a direct compression method with an effervescent approach. Poly ethylene Oxide (Polyox WSR 301, Polyox WSR 303, Polyox WSR 308) was chosen as the sustained-release polymer, while sodium bicarbonate served as the gas-generating agent. Preformulation study of API was performed using FTIR Spectroscopy. Drug excipient compatibility shows no interaction between drug and excipients. Trial batches initiated for screening of polymer. Prepared tablets were analyzed for various parameters like weight variation, hardness, thickness, friability, swelling and drug content, In-vitro drug release extended to 12 hours, with formulation T9 demonstrating 99% drug release, hence choosen for optimization using factorial design was done using DOE software. Factorial batches (F1-F9) with Polyox WSR 303, Sodium bicarbonate as Indipendent Variables showed significant outcomes. Factorial batch achieved desired drug release. Batch O1 was fine-tuned for drug release 99% over 12 hours and Floating Lag time 37 seconds. Higuchi's model fit best. The optimized batch O1 was subjected for Stability study and found stable for 1 month. Hence, O1 batch was the optimized batch.

Key Words: Tapentadol HCl, Polyox WSR 301, Polyox WSR 303, Polyox WSR 308, Sodium bicarbonate, Floating Tablets

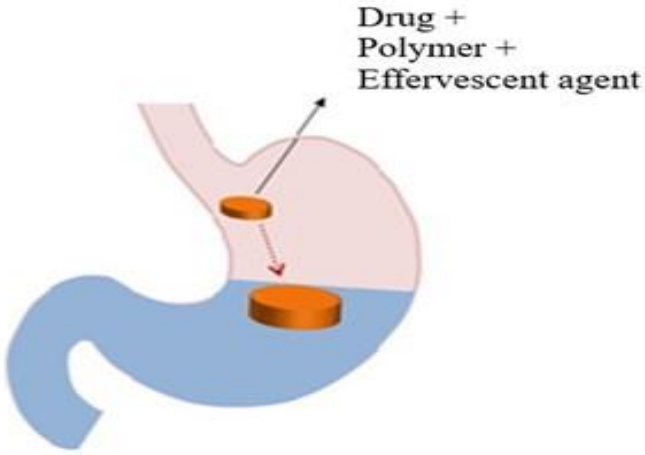
Introduction

The oral route of drug administration stands out as the most significant and convenient method for delivering medications. However, the potential for sustained drug release over extended periods hasn't been fully tapped due to variations in absorption across different sections of the gastrointestinal tract (GIT). Consequently, only a handful of drug delivery systems have been developed to target specific regions of the GIT, such as the stomach, upper small intestine, or colon.

The primary challenge in designing controlled-release oral dosage forms isn't just about extending drug delivery beyond 12 hours; It also entails keeping the dosage forms inside the upper small intestine or stomach for longer. The creation of dosage forms with extended gastric residence times (GRT), sometimes referred by the terms gastroretentive or gastroremaining dosage forms (GRDF), creates important new therapeutic opportunities.

Effervescent system

A One way to guarantee that a medication delivery system stays float in the stomach is to incorporate a floating chamber that can be occupied by inert gas, air, or vacuum. An organic solvent can volatilize or an effervescent reaction between organic acids and bicarbonate salts can introduce gas into the floating chamber



Materials and methods

Tapentadol HCl was obtained from Ami Lifescience, Vadodara, Poly Ethylene oxide from JRS Pharma, Mumbai. SMCC (Silicified Microcrystalline cellulose) from JRS Pharma, Mumbai Ethyl Cellulose, Magnesium Stearate, Talc, Lactose, All other ingredients from Chemdyes Corporation, Rajkot-360001. (Gujarat). Sodium Bicarbonate, Citric Acid from SD fine chemical, Ahmedabad.

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Method of Preparation of Buccal Tablets

The preliminary trials for polymer selection involved preparing tablets using different matrix-forming agents via direct compression technique. Blends comprising the drug, matrix-forming agent, gas-generating agent, and diluents were thoroughly mixed after passing through a 40# sieve. Talc and magnesium stearate were then added as glidant and lubricant, respectively. The blend was compressed using a tablet press machine.

Table 1 Formulation Table of Trial Batches of Buccal tablets

Ingredients (mg)	T1	T2	T3	T4	T5	T6	T7	T8	T9
Tapentadol HCl	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
Polyox WSR 301	25.0	-	-	75.0	-	-	-	-	-
Polyox WSR 303	-	25.0	-	-	75.0	-	50.0	50.0	50.0
Polyox WSR 308	-	-	25.0	-		75.0	-	-	-
Sod. Bicarbonate	20.0	20.0	20.0	20.0	20.0	20.0	20.0	10.0	30.0
Citric Acid	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
PVP K30	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
SMCC 90	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
Starlac	89.0	89.0	89.0	39.0	39.0	39.0	114.0	114.0	114.0
Talc	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Mg. stearate	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Total weight	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**

Table 2 Layout of Factorial Design

3^2 Full Factorial Designs		
Batch No.	**X1 Polyox WSR 303**	**X2 Sodium Bicarbonate**
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

Translation of coded level in actual limit			
Independent variables	**Real Value**		
	Low(-1)	**Medium(0)**	**High(+1)**
Polyox WSR 303 (mg) X1	40.0	50.0	60.0
Sodium Bicarbonate (mg) X2	25.0	30.0	35.0

- ***Independent variables***
  - ✓ X_1-Amount of Polyox WSR 303 (mg)
  - ✓ X_2-Amount of Sodium Bicarbonate (mg)
- ***Dependent variables***
  - ✓ Y1- % Drug release at 1 hour
  - ✓ Y2- Floating Lag time (sec)

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tapentadol HCl	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
Polyox WSR 303	40.0	40.0	40.0	50.0	50.0	50.0	60.0	60.0	60.0
Sod. Bicarbonate	25.0	30.0	35.0	25.0	30.0	35.0	25.0	30.0	35.0
SMCC 90	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
PVP K30	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Citric Acid	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Starlac	59.0	54.0	49.0	49.0	44.0	39.0	39.0	34.0	29.0
Talc	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Mg. stearate	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Total weight	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**	**250.0**

Table 3 Formulation Table of Factorial Batches of Buccal tablets

Methodology

Preformulation

Characterization of API: -

Organoleptic property:
This involves documenting the drug's hue and scent using precise language. and record the same in results and discussion chapter.

Flow Property:
The study examined the flow characteristics of API/powder blends. To determine bulk density, 10 grams of powder were carefully poured into a 50-milliliter measuring cylinder without compaction, and the volume of the powder was recorded. After tapping the powder 100 times, the volume was measured to obtain the desired tapped density. The powder mixtures' Carr's index (CI) & Hausner ratio (HR) were calculated using the measurements of powder densities.

Melting point:
The Melting Point Testing Apparatus: technique was incorporated into the device to determine the drug's (API) melting point.

Using a modern melting point apparatus, the following steps are needed to measure melting point:

- make sure the sample is completely dry and powdered
- put the sample in a capillary tube
- insert the capillary tube to the melting point apparatus
- quickly heat the sample to a predetermined temperature
- slow down the rate of temperature increase to see when the sample melts
- view the melting point through a viewing eyepiece
- digitally record the melting point.

Drug Excipient Compatibility Study

FTIR investigations were conducted to evaluate the compatibility between excipients and the drug. Samples of the pure drug and physical mixtures of excipients with the drug were analyzed using FTIR to assess their compatibility. The distinctive peaks corresponding to various functional groups were compared with established standard peaks to determine any discrepancies.

Calibration Curve

Preparation of Standard Calibration Curve of Tapentadol HCl

Principle: The Tapentadol HCl exhibits peak absorbance at 275 nm in 0.1 N HCl (1.2 pH).

Instrument used: UV - Vis 1700 Spectroscopy by Shimadzu, UV Spectrophotometer, Japan.

Procedure:

- Preparation of standard solution : 10 mg of Tapentadol HCl was precisely measured and dissolved in a small volume of 0.1 N HCl (pH 1.2) in a 100 ml volumetric flask. The solution was then diluted with 0.1 N HCl (pH 1.2) to achieve a concentration of 100 µg/ml (SS-I). From this solution, 10 ml was withdrawn and further diluted to 100 ml to obtain a concentration of 10 µg/ml (SS-II).
- Preparation of working standard solutions: Aliquots of 2 ml, 4 ml, 6 ml, 8 ml and 10ml from SS-II were pipetted into 10 ml volumetric flasks. The volume was adjusted with 0.1 N HCl (pH 1.2) to achieve final concentrations of 2, 4, 6, 8, and 10 µg/ml, respectively. The absorbance of each concentration was measured at 275 nm.

- A solution containing Tapentadol hydrochloride (10 µg/mL) from SS-II was scanned in the UV region to identify the wavelength.
- λmax: 275 nm
- Beer's range: 2-10µg/ml.

Evaluation Parameters of Tablets

(A) Pre compression Parameters: -

- **Bulk Density**:
  Computed using the formula that follows.

  Bulk density = Weight of powder / Bulk volume
- **Tapped Density**

  Tapped density = Weight of powder / Tapped volume

- **Compressibility Index (CI):**

  Carr's Compressibility index (%) = {(TD- BD) / TD} X 100.

Table 4 Scale of flow ability by Compressibility index

C.I.	Category	Hausner's Ratio
<10	Excellent	1.00–1.110
11 – 15	Good	1.12–1.180
16 – 20	Fair	1.19–1.250
21 – 25	Passable	1.26–1.340
26 – 31	Poor	1.35–1.450
32 – 37	Very poor	1.46–1.590
>38	Very very poor	>1.600

Hausner's Ratio:

Hausner's ratio = Tapped density / Bulk density

(B) Post Compression Parameters

Weight Variation

An electric digital balance was used to weigh twenty tablets of each formulation, and the average weight was determined.

Table 5 IP/BP/USP limit of weight variation test.

IP/BP Average weight of tablet (mg)	% Deviation	USP Average weight of tablet (mg)
130 or less	10.0	80 or less
From 130 to 324	7.5	From 80 to 250
More than 324	5.0	More than 250

Hardness

Hardness was assessed by diametrically compressing six tablets from each batch using a Monsanto hardness tester, and average values were subsequently computed.

Friability

Friability, which indicates tablet strength, was assessed using a Roche-type friabilator following this procedure: After twenty tablets were weighed precisely, they were put into the tumbling device, which turned at a speed of twenty-five revolutions per minute, lowering the tablets every six inches. The tablets were tumbling for four minutes, and a percentage of weight loss was computed by reweighing the tablets.

$$\% \text{ loss} = \text{Initial wt.} - \text{Final wt.} / \text{Initial wt.} \times 100$$

Thickness

Using vernier callipers, the thickness of the buccal tablets was measured. A random selection of ten tablets was made from each batch. and their thickness was individually assessed. The average thickness was then calculated from the recorded measurements.

Assay

Ten tablets were individually weighed and then pulverized. Next, an amount of powder equivalent to one tablet was weighed, and the drug was extracted in 0.1 N HCl. The resulting solution was filtered through a 0.45 µm membrane. After appropriate dilution, the absorbance was measured using a Shimadzu UV-1700 UV/Vis double-beam spectrophotometer.

Floating Lag Time and Total Floating Time

In vitro buoyancy was assessed using a beaker method. Tablets were placed in a 900 ml beaker containing 0.1 N HCl solution at 37±0.5ºC. The duration for tablets to rise to the surface of the medium and the time it took for the tablet to remain buoyant on the surface were recorded as floating lag time and total floating time, respectively.

Swelling index

Tablets' swelling index was measured in 0.1 N HCl. Tablets were weighed individually and given the W0 label. They were then individually put into glass beakers with 100 ml of 0.1 N HCl at 37±0.5ºC. The tablets were taken out of the beaker on a regular basis, and any extra surface water was wiped off with blotting paper before the pills were weighed again and recorded as Wt. Next, the swelling index was computed using the following formula.

$$\text{Swelling index} = (W_t - W_0 / W_0) \times 100$$

Where, W_t = weight after swelling

W_0 = weight before swelling

***In Vitro* Dissolution Studies**

Using USP apparatus II, the dissolution profile was investigated while the dissolution medium (900 ml of 0.1N HCl) was kept at 37°C ± 0.5°C at 50 rpm. Each batch of pills had six that were put into separate baskets with the HCl solution within. Over the course of 12 hours, 10 ml samples were taken out every hour. A filter was applied to these samples. These solutions' absorbance was determined using a UV spectrophotometer.

Drug Release Kinetic Study

The zero order, first order, Korshmeyer and Papps, and Higuchi equation models were among them. Plotting the obtained data using the following models allowed us to study the release kinetics: Higuchi's model (Equation 3), which shows the cumulative percentage of drug released against the square root of time; zero order, which represents cumulative drug release over time (Equation 1); and first order, which shows the log cumulative percentage of remaining drug versus time (Equation 2). Drugs dissolved from pharmaceutical formulations that release the drug gradually without disaggregation are described by zero order kinetics.

$$Q_1 = Q_0 + K_0 t \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots 1$$

Q_0 is the starting concentration of drug in solution, Q_1 is the amount of drug dissolved at time t, and K_0 is the zero-order rate constant, given in concentration units over time. Hours of time are represented by the variable t. A concentration versus time plot graphed would connect the axes' origin and produce a straight line with a slope equal to K_0.First order model has been used to describe absorption and elimination of drugs. The following equation express this model.

$$\text{Log } Q_1 = \text{Log} Q_0 + (K_1 t / 2.303) \ldots\ldots\ldots\ldots\ldots\ldots 2$$

where Q_0 is the starting drug concentration in the solution, K_1 is the first order release constant, and Q_1 is the amount of drug released in time t. This will result in a linear graph showing the decimal logarithm of the amount of dug that has been released over time.

In order to investigate the release of pharmaceuticals that are water soluble and low solubility when incorporated into semi-solid or solid matrices, Higuchi created a number of models. Giving rise to the following expression.

$$Q = K_H t^{1/2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots 3$$

where t is the time in hours, Q is the amount of drug released at time t, and KH is the Higuchi dissolution constant reflecting the system's design characteristics. Therefore, the reciprocal of the square root of time and the medication release rate are proportionate. According to Higuchi, drug release is a diffusion mechanism that is time-dependent and based on Fick's law, square root.

Mechanism of Drug Release : Data from the dissolution research were plotted in Korsmeyer Peppa's equation as log cumulative percentage of drug released vs. log time in order to assess the mechanism of drug release from tablets. The exponent n was then determined by calculating the slope of the straight line.

$$F = (M_t / M) = K_m t^n \ldots\ldots\ldots\ldots\ldots\ldots 4$$

where K_m is a constant dependent on the geometry of the dosage form, 'n' is the slope of the linear plot, Mt is the drug release at time t, F is the fraction of drug release at time t, and M is the total amount of medication in the dosage form. The releasing mechanism is indicated by the value of n.

When the exponent value n is equal to 0.5 in Fickian diffusion, and when it is between 0.5 and 1.0 in non-Fickian diffusion, it is considered abnormal. When the exponent value is n=1, it denotes a standard zero-order release or Case-II Transport.

Stability Study

For a month, the optimised batch of floating tablets was subjected to accelerated stability testing in a humidity chamber with a temperature of 40°C and a relative humidity of 75%. The best batch of tablets were evaluated for appearance, drug content, floating qualities, and in vitro drug release characteristics before being wrapped in aluminium foil pouches.

Results & discussion

Preformulation Study

Table 6 API properties

Sr. No.	Characteristic Properties		Observation/Result
1	**Organoleptic Characteristics**	Colour of API	It is White colour crystalline Powder
		Odour of API	It is Odourless powder
		Taste of API	It is Tasteless powder
2	**Flow Properties**	Bulk density of API (g /ml)	0.58 ± 0.01
		Tapped density of API (g /ml)	0.70 ± 0.01
		Carr's index (%) of API	17.1 ± 0.02
		Hausner's ratio of API	1.21 ± 0.01
		Angle of repose (θ°) of API	38.6 ± 0.2
3	**Solubility**	It was observed that API was freely soluble in water and 0.1 N HCL at room temperature.	
4	**Melting Point**	206-209 °C	

Standard Calibration Curve of Tapentadol HCl

The standard calibration curve was prepared in 0.1 N HCl (pH 1.2). The λ_{max} found 275 nm. Please refer below figure for λ_{max}.

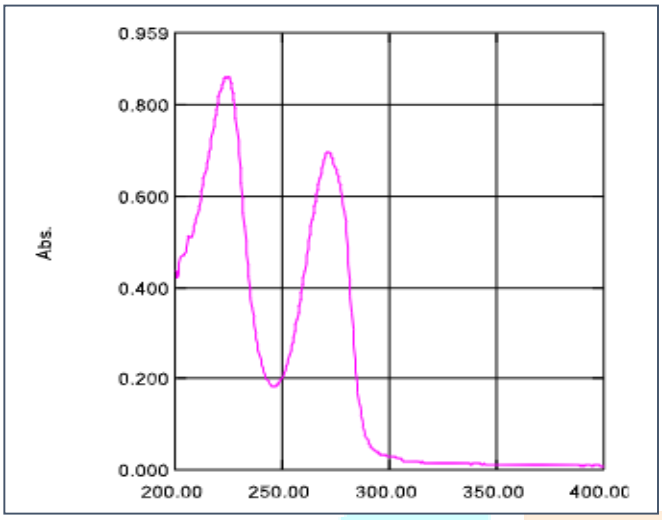

Figure 1 $\lambda_{max}$of Tapentadol HCl in 0.1 N H

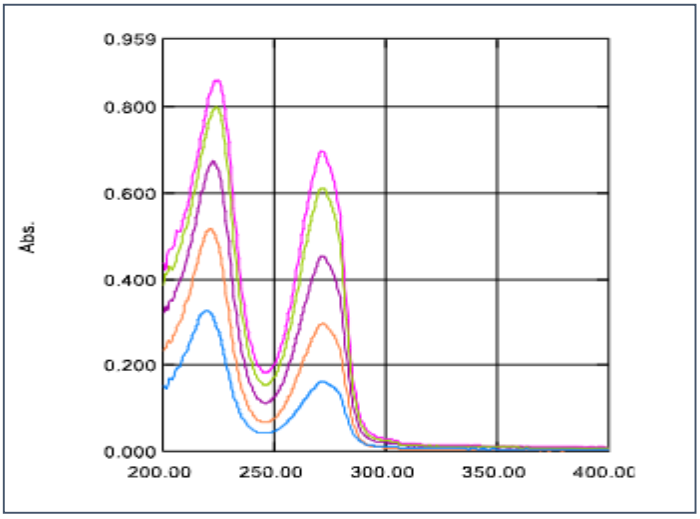

Figure 2 Overlay plot of Tapentadol HCl in 0.1 N HCl

Table 7 Standard calibration curve Tapentadol HCl in 0.1 N HCl

Concentration (µg/ml)	Absorbance (Average) ± SD
0.0	0.0 ±0.000
2	0.154 ± 0.001
4	0.281 ± 0.001
6	0.428 ± 0.002
8	0.560 ± 0.003
10	0.703 ± 0.002

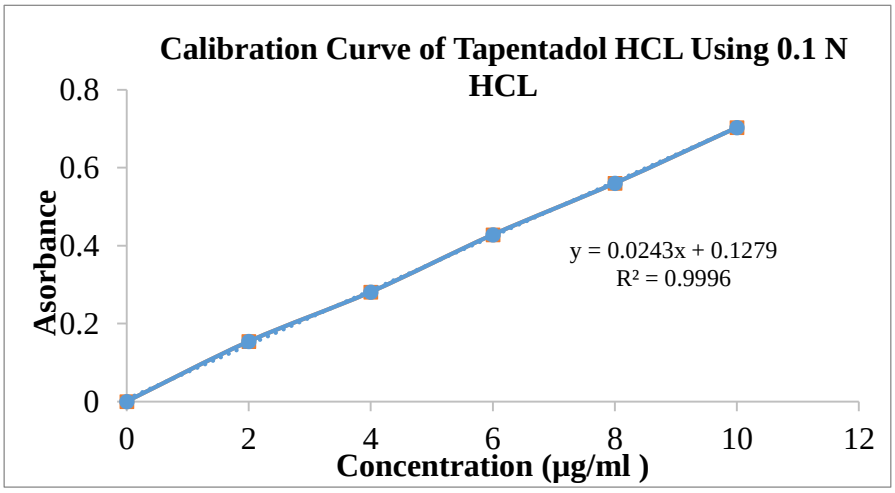

Figure 3 Calibration curve of Tapentadol HCl in 0.1 N HCl

Drug- excipient compatibility studies

The FTIR spectra of both the pure drug and the optimized formulation are depicted in figures below. Upon examination of these figures, it was determined that no interactions between the drug and excipients were observed. All characteristic peaks of the pure drug remained unchanged in the final formulation.

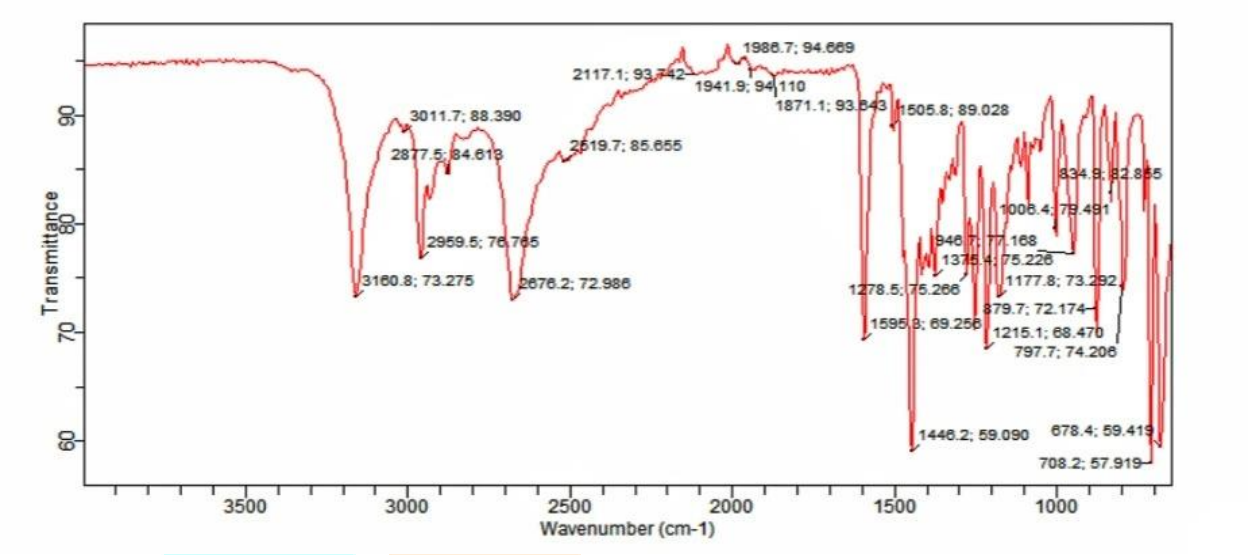

Figure 4 FTIR spectra of Tapentadol HCl

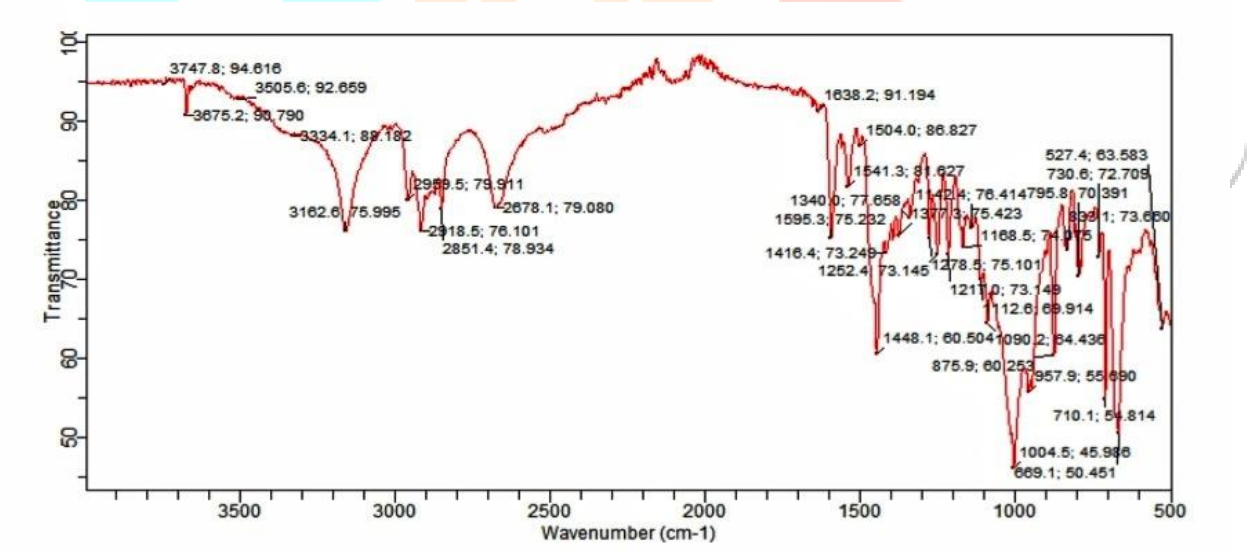

Figure 5 FTIR of Physical Mixture of Optimized Formulation

Table 8 Interaction studies through IR spectroscopy

Stretching	Tapentadol HCl	Formulation
	Peak cm^{-1}	Peak cm^{-1}
C–N Stretching	1006.4	1004.5
C–O Stretching	1278.5	1278.5
C=C Stretching	1595.8	1595.3
N–H Stretching	2676.2	2678.1
C–H Stretching	2959.5	2959.5
O–H Stretching	3160.8	3162.6

Conclusion: Based on the FTIR study findings presented above, it was concluded that there were no notable interactions observed between the drug and excipients. Therefore, the drug and other excipients are deemed compatible with each other.

Pre compression Parameters of Trial Batches

Table 8 Result of Pre compression parameters of Trial Batches

Batch	Bulk density (g/ml)(n=3)	Tapped density (g/ml)(n=3)	Carr's index (%) (n=3)	Hausner's ratio (n=3)	Angle of repose (θ°) (n=3)
T1	0.54 ± 0.02	0.61 ± 0.03	11.48 ± 0.01	1.13 ± 0.02	32.25 ± 0.05
T2	0.48 ± 0.03	0.52 ± 0.05	7.69 ± 0.02	1.08 ± 0.01	35.22 ± 0.08
T3	0.47 ± 0.05	0.55 ± 0.03	14.55 ± 0.04	1.17 ± 0.02	31.12 ± 0.07
T4	0.57 ± 0.07	0.60 ± 0.04	5.00 ± 0.07	1.05 ± 0.01	34.26 ± 0.08
T5	0.47 ± 0.04	0.54 ± 0.04	12.96 ± 0.05	1.15 ± 0.02	34.15 ± 0.07
T6	0.42 ± 0.05	0.54 ± 0.02	16.00 ± 0.06	1.19 ± 0.02	31.19 ± 0.05
T7	0.51 ± 0.08	0.56 ± 0.05	8.93 ± 0.04	1.10 ± 0.01	34.56 ± 0.04
T8	0.52 ± 0.02	0.58 ± 0.04	10.34 ± 0.05	1.12 ± 0.01	33.75 ± 0.03
T9	0.47 ± 0.04	0.54 ± 0.02	12.96 ± 0.05	1.15 ± 0.01	32.84 ± 0.03

It can be concluded from the flow property data above that the blended flow is of a good nature and handles compression smoothly.

Evaluation of post compression parameters Trial Batches

Post-compression parameters of trial batches T1-T9 were evaluated, including weight variation, thickness, hardness, and friability. All batches successfully passed the weight variation test, demonstrating uniformity in tablet weight. Additionally, the tablets exhibited adequate hardness to withstand mechanical stress. Friability tests revealed that all batches had a friability below 1%, meeting the formulation's requirements. Furthermore, the tablets demonstrated uniform thickness across all batches. In conclusion, the physical parameters of the tablets were deemed satisfactory for all trial batches.

Table 9 Results of post compression parameters of Trial Batches

Batch	Weight variation test (mg) (n=3)	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3)	Friability (%) (n=3)
T1	250 ± 2.3	4.52 ± 0.13	4.9 ± 0.5	0.61 ± 0.22
T2	255 ± 2.1	4.51 ± 0.11	4.8 ± 0.3	0.63 ± 0.19
T3	250 ± 2.6	4.48 ± 0.15	4.9 ± 0.4	0.47 ± 0.13
T4	255 ± 2.2	4.51 ± 0.08	5.1 ± 0.6	0.84 ± 0.17
T5	250 ± 2.7	4.49 ± 0.10	5.7 ± 0.2	0.50 ± 0.26
T6	250 ± 1.8	4.50 ± 0.12	5.5 ± 0.3	0.81 ± 0.11
T7	250 ± 2.5	4.52 ± 0.11	4.9 ± 0.7	0.62 ± 0.16
T8	255 ± 2.5	4.51 ± 0.16	5.3 ± 0.3	0.64 ± 0.12
T9	250 ± 2.0	4.51 ± 0.13	5.1 ± 0.6	0.66 ± 0.23

Table 10 Results of post compression parameters of Trial Batches

Batch	Drug Content (%) (n=3)	Swelling Index (%) (n=3)	Floating Lag Time (sec) (n=3)	Total Floating Time (hr.) (n=3)
T1	97.9 ± 2.1	51.6 ± 2.1	65 ± 2	4 ± 0.2
T2	99.1 ± 1.5	62.4 ± 2.4	62 ± 2	5 ± 0.3
T3	99.5 ± 2.4	68.5 ± 3.3	72 ± 3	4 ± 0.6
T4	99.0 ± 2.6	58.2 ± 2.5	68 ± 3	12 ± 0.2
T5	98.8 ± 1.4	62.5 ± 2.8	75 ± 4	>12 ± 0.5
T6	98.7 ± 2.9	54.6 ± 3.4	78 ± 4	>12 ± 0.5
T7	97.5 ± 1.8	68.9 ± 2.1	75 ± 2	12 ± 0.7
T8	99.6 ± 2.8	68.6 ± 3.1	85 ± 5	12 ± 0.4
T9	98.2 ± 2.1	69.4 ± 2.6	48 ± 1	12 ± 0.2

In Vitro Drug Release Study

Table 11 Drug release of Trial Batches

Time in hr.	T1	T2	T3	T4	T5	T6	T7	T8	T9
1	40.3± 2.4	37.9± 2.9	35.8± 2.9	22.9± 2.5	20.8± 2.4	19.2± 2.3	26.7± 2.6	25.9± 2.4	32.5± 2.8
2	59.7± 1.8	51.8± 2.7	48.8± 2.5	31.8± 2.3	31.5± 2.9	28.9± 2.1	37.8± 2.4	30.9± 1.9	40.5± 2.5
3	79.8± 1.1	66.0± 2.1	60.5±2. 4	39.5±2. 1	37.9± 2.7	34.8± 2.9	43.5± 2.9	35.9± 1.4	48.9± 2.1
4	99.0±1. 9	84.2± 2.3	79.8±2. 4	45.5±2. 0	42.5±2. 9	39.8± 2.7	50.7± 2.1	43.7± 1.9	56.8± 2.9
5	-	99.2±2. 4	87.3±2. 1	50.3±1. 8	45.9±2. 7	42.3± 2.4	58.6± 1.9	51.9±2. 5	64.8± 2.8
6	-	-	99.9±1. 7	55.6± 2.1	48.7±2. 6	46.4± 2.1	65.2±2. 7	58.4±2. 4	71.8± 2.5
7	-	-	-	62.8±2. 8	52.4±2. 5	49.2±2. 8	73.4±2. 4	66.1±1. 9	76.4±2. 9
8	-	-	-	70.4±2. 4	56.8±2. 3	52.9±2. 4	79.9±2. 1	71.3±1. 7	80.9±2. 5
9	-	-	-	75.9±2. 1	60.2±2. 1	54.8±2. 1	84.5±2. 0	77.2±1. 5	84.5±2. 1
10	-	-	-	81.8±1. 7	62.5±1. 9	56.6±2. 0	88.6±1. 8	81.3±1. 3	88.6±1. 6
11	-	-	-	85.3±1. 6	64.9±1. 7	59.9±1. 8	93.7±1. 4	85.6±1. 1	93.7±1. 4
12	-	-	-	88.1±1. 2	68.4±1. 2	62.5±1. 5	96.4±1. 1	93.5±0. 8	99.8±1. 1

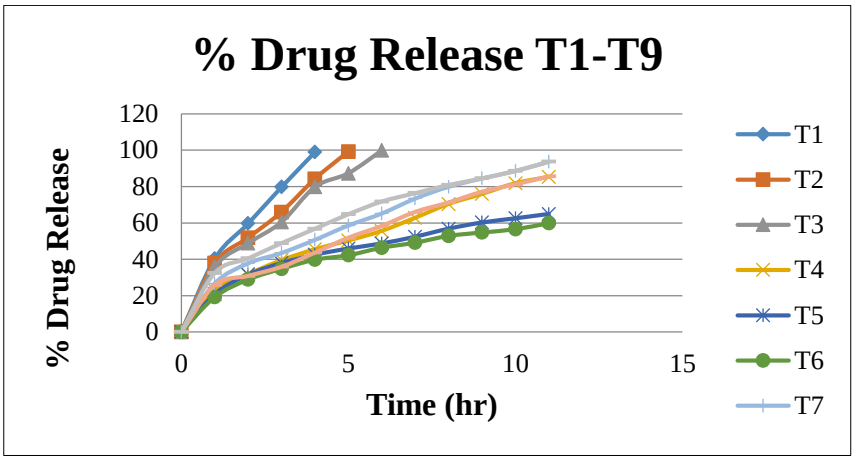

Figure 6 Drug release of Batch T1-T9 of Trial Batches

Evaluation of factorial batches

Powder blend of factorial batches F1-F9 checked for pre-compression parameters. Observed results are mentioned in following table. From the below table it concluded that the all batches have a good flow properties.

Table 12 Results of Pre compression parameters of factorial batches

Batch	Bulk density (g/ml) (n=3)	Tapped density (g/ml)(n=3)	Carr's index (%) (n=3)	Hausner's ratio (n=3)	Angle of repose (θ°) (n=3)
F1	0.49 ± 0.04	0.58 ± 0.08	15.52 ± 0.03	1.18 ± 0.02	32.14 ± 0.08
F2	0.47 ± 0.05	0.54 ± 0.08	12.96 ± 0.04	1.15 ± 0.02	31.04 ± 0.07
F3	0.48 ± 0.06	0.59 ± 0.07	18.64 ± 0.02	1.23 ± 0.01	33.56 ± 0.05
F4	0.58 ± 0.05	0.64 ± 0.05	9.38 ± 0.03	1.10 ± 0.01	31.45 ± 0.06
F5	0.47 ± 0.08	0.55 ± 0.05	12.96 ± 0.04	1.15 ± 0.01	32.56 ± 0.04
F6	0.43 ± 0.03	0.49 ± 0.04	12.24 ± 0.06	1.14 ± 0.01	32.84 ± 0.06
F7	0.46 ± 0.07	0.52 ± 0.07	11.54 ± 0.02	1.13 ± 0.01	31.54 ± 0.04
F8	0.51 ± 0.03	0.57 ± 0.05	10.53 ± 0.04	1.12 ± 0.02	33.45 ± 0.05
F9	0.52 ± 0.02	0.59 ± 0.07	15.25 ± 0.08	1.18 ± 0.01	31.15 ± 0.02

Table 13 Results of post compression parameters of factorial batches

Batch	Weight variation test (mg) (n=3)	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3)	Friability (%) (n=3)
F1	252 ± 2.2	4.53 ± 0.10	4.9 ± 0.3	0.82 ± 0.12
F2	251 ± 2.8	4.53 ± 0.14	5.0 ± 0.2	0.65 ± 0.08
F3	250 ± 2.9	4.52 ± 0.19	4.8 ± 0.4	0.87 ± 0.13
F4	253 ± 2.8	4.51 ± 0.09	5.1 ± 0.2	0.67 ± 0.11
F5	251 ± 2.5	4.50 ± 0.12	5.0 ± 0.5	0.61 ± 0.18
F6	250 ± 3.1	4.48 ± 0.18	5.2 ± 0.2	0.62 ± 0.17
F7	252 ± 2.8	4.47 ±0 .17	5.4 ± 0.3	0.52 ± 0.12
F8	254 ± 1.9	4.45 ± 0.12	5.6 ± 0.1	0.47 ± 0.15
F9	252 ± 2.4	4.46 ± 0.16	5.4 ± 0.4	0.51 ± 0.14

Table 15 Results of post compression parameters of factorial batches

Batch	Drug Content (%) (n=3)	Swelling Index (%) (n=3)	Floating Lag Time (sec) (n=3)	Total Floating Time (hr.)
F1	96.8 ± 3.1	62.5 ± 1.9	64 ± 2	9.0
F2	98.7 ± 2.9	63.7 ± 2.5	38 ± 3	9.0
F3	98.6 ± 2.7	64.1 ± 2.1	25 ± 2	9.0
F4	99.8 ± 2.2	67.6 ± 2.6	70 ± 3	12.0
F5	97.5 ± 1.8	69.9 ± 2.1	45 ± 2	12.0
F6	99.1 ± 2.7	68.2 ± 2.9	40 ± 2	12.0
F7	98.3 ± 2.9	70.3 ± 3.4	75 ± 3	>12.0
F8	99.4 ± 1.4	72.5 ± 2.7	60 ± 2	>12.0
F9	98.6 ± 1.8	71.8 ± 3.2	48 ± 2	>12.0

Drug release

Drug release of factorial batches was performed to check the impact of the amount of polymer and efferent agent. Based on results it found that the amount of polymer change the release profile of the tablets. The actual impact was checked by using factorial design. The comparative plot was shown in below figure.

Table 14 Drug release study of factorial batches

Time in hr.	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	27.1±2.9	30.4±2.1	34.5±2.4	24.3±2.1	28.5±2.1	29.2 ± 2.4	19.2±2.9	22.4±2.5	24.3±2.1
2	40.3±2.2	43.2±2.8	46.3±2.9	35.8±2.8	39.5±2.7	41.5±2.1	27.9±2.7	29.5±2.4	32.8±2.9
3	52.3±2.0	55.9±2.4	58.9±2.7	42.8±2.7	44.1±2.5	47.3±2.9	35.8±2.6	37.1±2.1	38.9±2.5
4	61.9±2.8	64.4±2.9	69.2±2.6	49.6±2.1	51.5±2.9	53.9±2.5	43.2±2.4	45.9±2.9	47.2±2.3
5	71.6±2.5	74.9±2.5	78.5±2.3	57.1±2.9	59.4±2.7	61.4±2.1	50.1±2.2	52.2±2.7	54.9±2.1
6	80.9±2.1	82.5±2.4	85.1±2.0	63.5±2.5	65.7±2.4	67.9±2.9	57.3±2.0	59.7±2.4	61.7±2.9
7	88.7±2.9	90.9±2.1	92.5±2.8	70.8±2.2	73.9±2.1	75.3±2.5	64.2±2.7	66.3±2.1	68.9±2.5
8	95.8±2.5	97.3±2.9	98.6±1.9	77.9±2.9	80.5±2.8	83.1±2.2	69.8±2.5	71.2±1.9	73.2±2.1
9	99.9±2.1	99.2±2.5	99.7±1.5	82.6±2.7	84.8±2.5	86.9±2.1	75.9±2.4	77.9±1.8	78.6±1.9
10	-	-	-	88.7±2.5	90.5±2.1	93.4±1.9	79.6±2.1	82.2±1.5	83.9±1.5
11	-	-	-	95.6±2.4	96.7±1.9	97.9±1.5	83.1±2.0	84.9±1.1	86.5±1.2
12	-	-	-	98.2±2.1	99.3±1.5	99.5±1.1	86.3±1.7	87.3±1.0	89.2±1.0

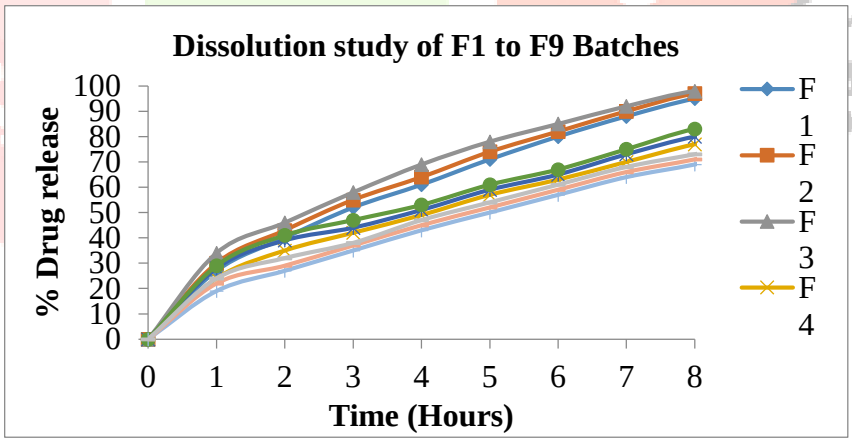

Figure 7 % Drug release of factorial batch F1-F2

Drug Release Kinetic Study

In vitro drug release study data was fitted in kinetic models and results obtained were shown in below table 17. Formulation was best fitted with **Korsmeyer Peppas** model and mechanism of drug release was found to be Non-Fickian type of diffusion.

Table 17 Drug Release Kinetic Study of factorial batches F1-F9

Formulation code	Zero Order	First Order	Higuchi	Korsmeyer Peppas model	
	R^2	R^2	R^2	R^2	N
F1	0.9923	0.9575	0.9986	0.9992	0.597
F2	0.9877	0.9537	0.9979	0.9987	0.553
F3	0.9826	0.9500	0.9970	0.9979	0.508
F4	0.9975	0.9712	0.9961	0.9975	0.546
F5	0.9975	0.9787	0.9970	0.9927	0.500
F6	0.9971	0.9761	0.9944	0.9947	0.485
F7	0.9983	0.9691	0.9960	0.9983	0.634
F8	0.9981	0.9756	0.9947	0.9945	0.585
F9	0.9972	0.9772	0.9945	0.9936	0.544

Analysis of factorial design

The obtained results were compiled for analysis using factorial design. The factors and responses tabulated in software than analysis was done using below table.

Table 18 Factorial design analysis table

Batch	Independent variable		Dependent Variables	
	A (Polyox WSR 303) mg	B (Sodium Bicarbonate) Mg	Y_1 (% Drug release at 1 hour)	Y_3 Floating Lag time(sec)
F1	40.0	25.0	27.0	64.0
F2	40.0	30.0	30.0	38.0
F3	40.0	35.0	34.0	25.0
F4	50.0	25.0	24.0	70.0
F5	50.0	30.0	28.0	45.0
F6	50.0	35.0	29.0	40.0
F7	60.0	25.0	19.0	75.0
F8	60.0	30.0	22.0	60.0
F9	60.0	35.0	24.0	48.0

ANOVA for Quadratic model

Response 1: (% Drug release at 1 hour)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	164.33	5	32.87	59.16	0.0034	Significant
A-Polyox WSR 303	112.67	1	112.67	202.80	0.0008	
B-Sodium Bicarbonate	48.17	1	48.17	86.70	0.0026	
AB	1.0000	1	1.0000	1.80	0.2722	
A^2	2.00	1	2.00	3.60	0.1540	
B^2	0.5000	1	0.5000	0.9000	0.4128	
Residual	1.67	3	0.5556			
Cor Total	166.00	8				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 59.16 implies the model is significant. There is only a 0.34% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Final Equation in Terms of Actual Factors

(% Drug release at 1 hour	=
-26.00000	
+0.866667	Polyox WSR 303
+2.26667	Sodium Bicarbonate
-0.010000	Polyox WSR 303 * Sodium Bicarbonate
-0.010000	Polyox WSR 303^2
-0.020000	Sodium $Bicarbonate^2$

Y=-26.00000+0.866667+2.26667-0.010000-0.010000-0.020000

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

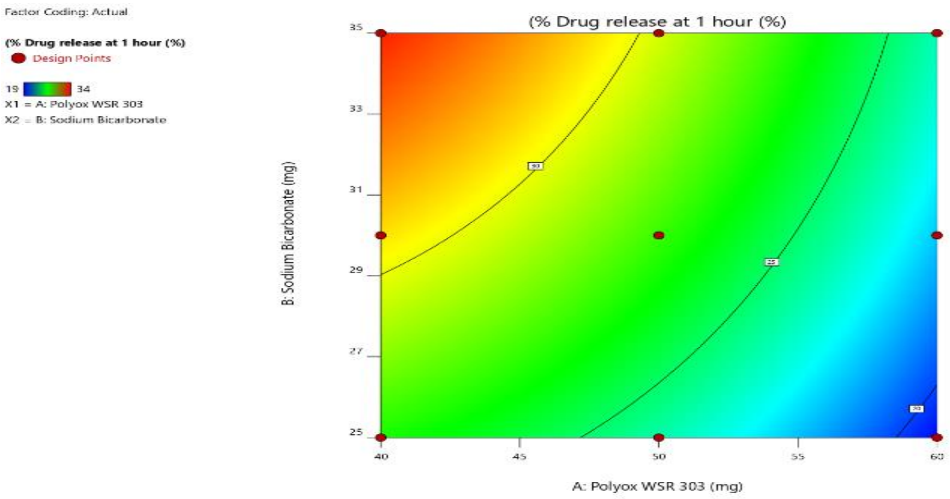

Figure 8 Contour Plot for drug release

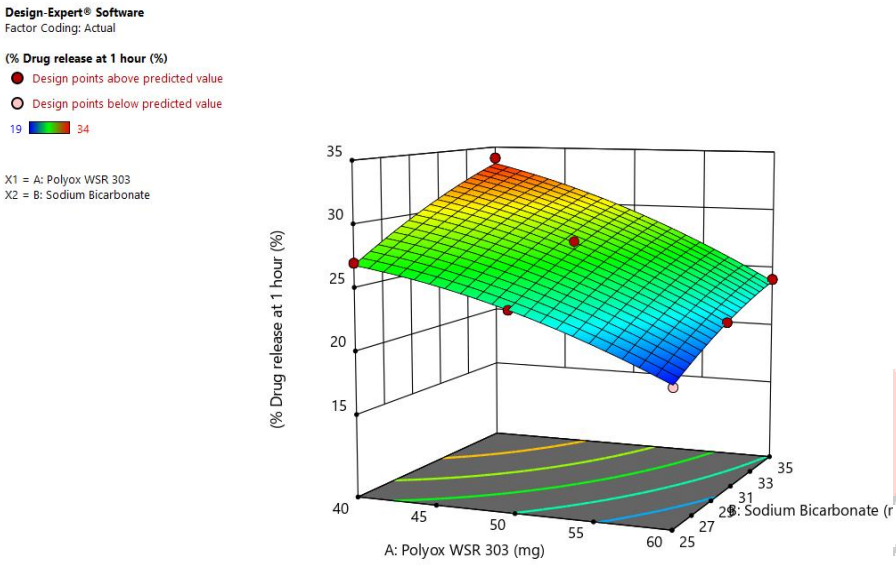

Figure 9 Surface Plot for drug release

ANOVA for Quadratic model

Response 2: Floating Lag time

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2166.67	5	433.33	47.56	0.0047	Significant
A-Polyox WSR 303	522.67	1	522.67	57.37	0.0048	
B-Sodium Bicarbonate	1536.00	1	1536.00	168.59	0.0010	
AB	36.00	1	36.00	3.95	0.1410	
A^2	0.0000	1	0.0000	0.0000	1.0000	
B^2	72.00	1	72.00	7.90	0.0672	
Residual	27.33	3	9.11			
Cor Total	2194.00	8				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 47.56 implies the model is significant. There is only a 0.47% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Final Equation in Terms of Actual Factors

Floating Lag time	=
+403.0000	
-0.86666	Polyox WSR 303
-20.6000	Sodium Bicarbonate
+0.06000	Polyox WSR 303 * Sodium Bicarbonate
+7.71246E-1	Polyox WSR 303²
+0.24000	Sodium Bicarbonate²

$$Y = 403.0000-0.86666-20.6000+0.060001+7.71246E-1+ 0.24000$$

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

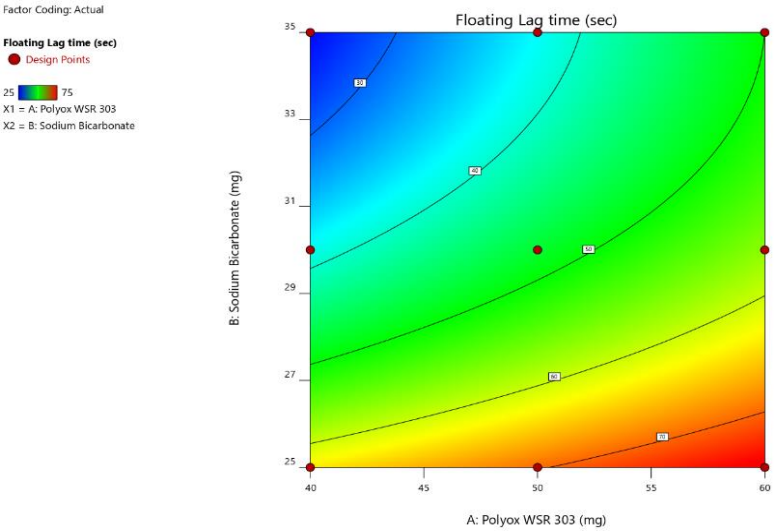

Figure 10 Contour Plot for Floating Lag Time

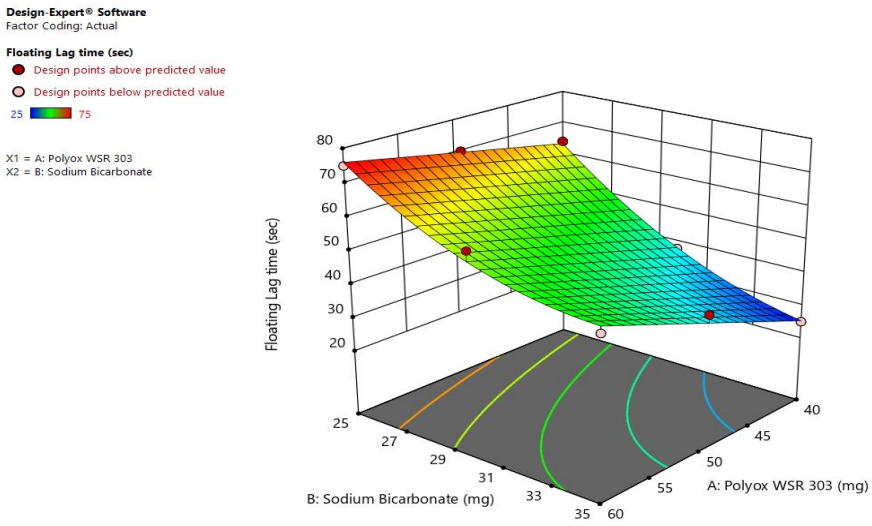

Figure 11 Surface Plot for Floating Lag Time

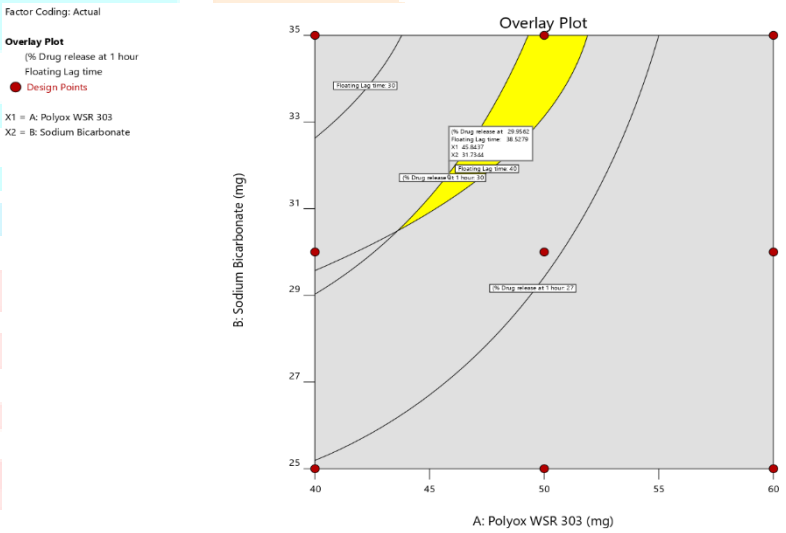

Figure 12 Overlay Plot

Check point batch analysis (Validation of design)

Validation of model

As seen in Table 6.15, a checkpoint batch was created using the desirability function. In order to verify the accuracy of the prediction, a checkpoint batch including C1 and C2 was generated and subjected to the same evaluation guidelines as the other batches. Data from the response and the necessary data were compared. The target response parameters and the obtained response variables of the check point batch were compared. It was allowed to have bias for observed vs projected responses.

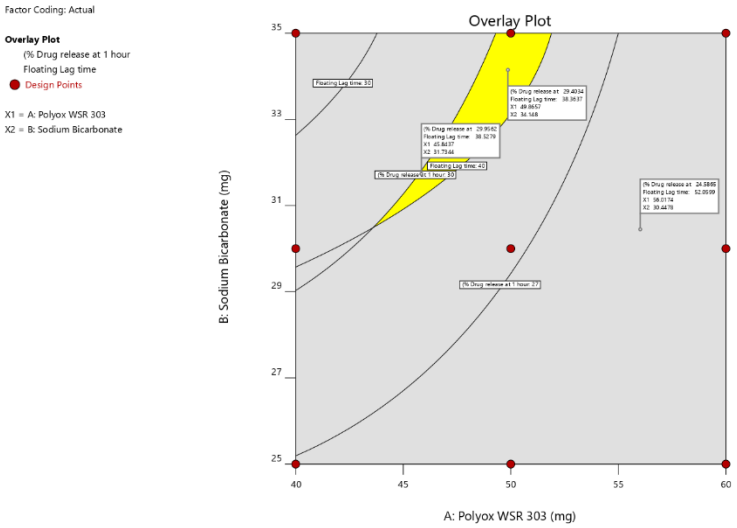

Figure 13 Overlay Plot for check point batch

Table 19 Check point batch

Batch	Amount of Polyethylene Oxide (mg)	Amount of Sodium Bicarbonate (mg)	% Drug release at 1 hour		
			Predicted	Observed	% Bias
C1	49.80	34.10	29.40	29.10	1.010
C2	56.00	30.40	24.50	24.90	0.980
Batch	**Amount of Polyethylene Oxide (mg)**	**Amount of Sodium Bicarbonate (mg)**	**Floating Lag time (sec)**		
			Predicted	**Observed**	**% Bias**
C1	49.80	34.10	38.0	37.0	1.020
C2	56.00	30.40	52.0	53.0	0.980

Selection of optimized batch

Finally, optimized batch was taken from the overlay plot and complete analysis was done and finally loaded for stability study.

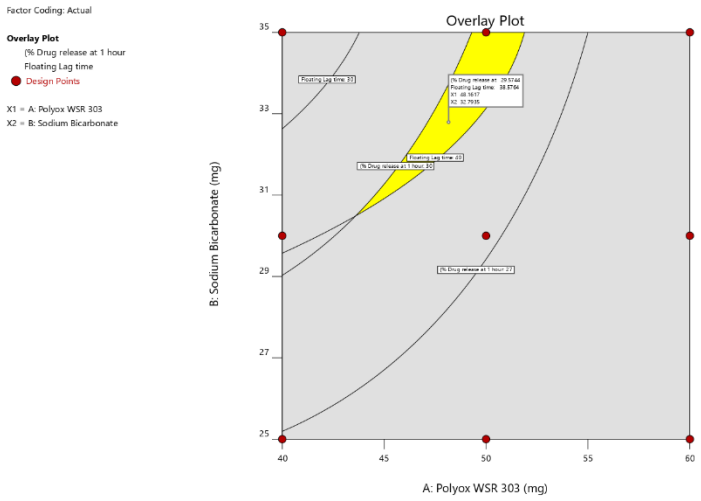

Figure 14 Overlay Plot for optimized batch

Table 20 Composition of Optimized batch O1

Ingredients (mg)	O1
Tapentadol HCl	50.0
Polyox WSR 303	48.10
Sod. Bicarbonate	32.70
Citric Acid	15.0
PVP K30	5.0
SMCC 90	50.0
Starlac	43.20
Talc	2.0
Mg. stearate	4.0
Total weight	**250.0**

Table 21 Results of optimized batch O1

Evaluation Parameters	Results	
Weight variation (mg)	251 ± 1.6	
Thickness(mm)	4.6 ± 0.3	
Hardness(kg/cm^2)	5.4 ± 0.2	
Friability (%)	0.42 ± 0.02	
Drug Content (%)	99.6 ± 1.3	
Swelling Index(%)	67.3 ± 1.1	
Floating Lag Time (sec)	37 ± 3	
Total Floating Time (hr.)	12.00 hours	
% Drug Release	**Time (hour)**	**% Drug Release**
	0.0	0
	1.0	29.6±3.9
	2.0	37.9±3.2
	4.0	53.8±2.8
	6.0	67.5±2.6
	8.0	80.4±1.7
	10.0	91.7±1.4
	12.0	99.5±0.9
Drug Release Kinetic Study	**Kinetic Model**	**R^2 value**
	Zero Order	0.9946
	First Order	0.9677
	Higuchi	**0.9976**
	Peppas	0.9964

The optimized batch O1 was prepared and evaluated. The prepared tablets were found satisfactory in physical as well as chemical evaluation. The tablets have uniform drug distribution hence drug content was found satisfactory. Weight variation also found well within acceptable range. Thickness was found uniform. Floating properties also found satisfactory. Drug release profile of 12 hrs. Found 99.2%. Finally optimized batch O1 was loaded for stability for 1 month.

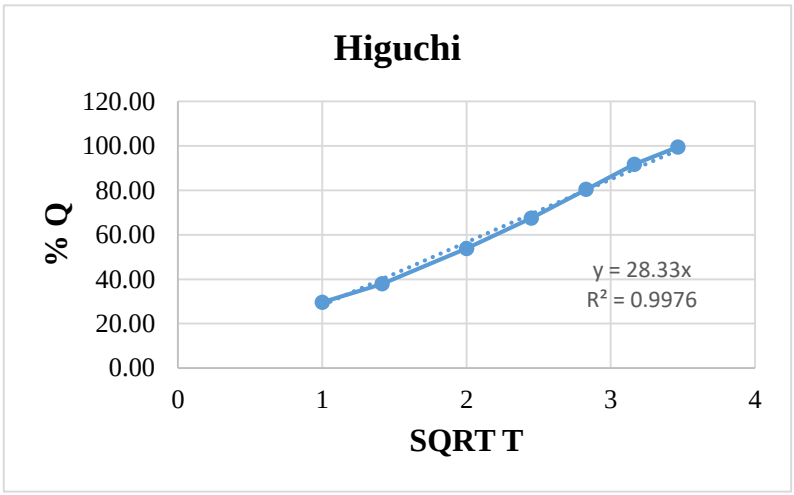

Figure 15 Higuchi graph

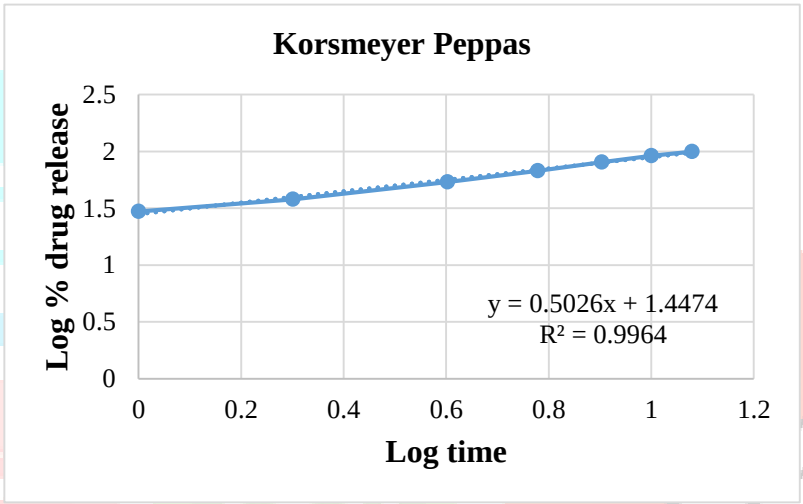

Figure 16 Korsmeyer Peppas graph

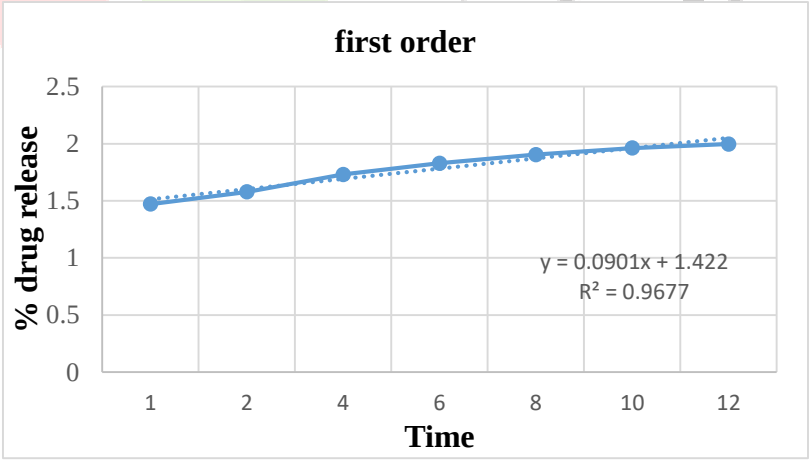

Figure 17 Fist order graph

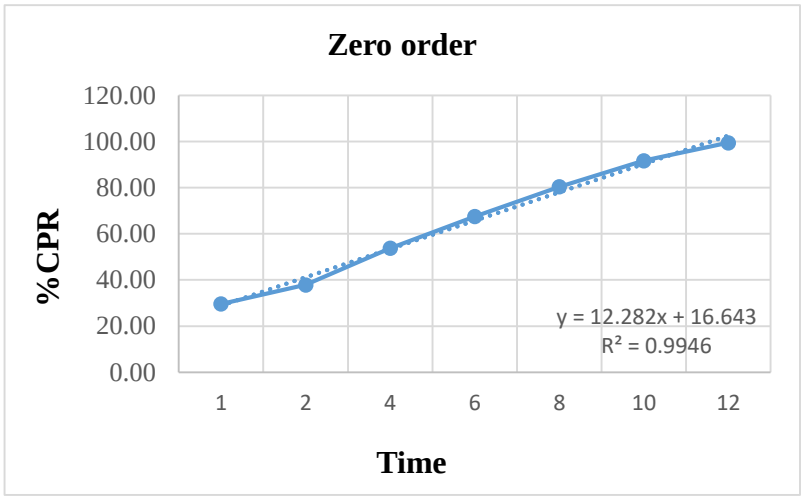

Figure 18 Zero order graph

Stability Study

The optimized batch, O1, which exhibited superior results compared to other batches, was chosen for stability assessment. The stability study was conducted for one month under conditions of 40°C temperature and 75% relative humidity in a stability chamber. After the one-month duration, samples were withdrawn for analysis. The results indicated no alteration in the in-vitro drug release profile after 12 hours. Furthermore, the stability study demonstrated that the percentage drug content remained within the acceptable range. Additionally, there were no observable changes in the outer appearance of the tablets.

Table 22 Results of stability study of batch O1

Batch	Time Period	Appearance	Drug Content (%) (n=3)	Floating Lag Time (sec) (n=3)	*In-vitro* drug release at 12 hrs. (n=3)
O1	Initial	White tablet	99.6 ± 1.3	37 ± 3	99.5 ± 0.9
	After 30 days	White tablet	99.2 ± 1.8	39±4	99.3 ± 1.6

Conclusion

Preparation Method: Floating tablets of Tapentadol HCl were prepared via direct compression using an effervescent approach.

Ingredients: Poly ethylene Oxide (Polyox WSR 303) served as the sustained release polymer. Sodium bicarbonate functioned as the gas-generating agent.

Effects of Polymer Concentration: Increasing polymer concentration decreased the drug release profile.

Effects of Sodium Bicarbonate Amount: Increasing sodium bicarbonate amount decreased floating lag time.

Conclusion: Polyox WSR 303 and sodium bicarbonate, in appropriate concentrations, effectively developed sustained-release floating tablets of Tapentadol HCl. Preformulation study of API was performed using FTIR Spectroscopy. Drug excipient compatibility shows no interaction between drug and excipients. Trial batches initiated for screening of polymer. prepared tablets were analyzed for various parameters like weight variation, hardness, thickness, friability, swelling and drug content, In-vitro drug release extended to 12 hours, with formulation T9 demonstrating 99% drug release, hence choosen for optimization using

factorial design was done using DOE software. Factorial batches (F1-F9) with Polyox WSR 303, Sodium bicarbonate as Indipendent Variables showed significant outcomes. Factorial batch achieved desired drug release. Batch O1 was further refined for drug release 99% over 12 hours and Floating Lag time 37 seconds. Higuchi's model fit best. The optimized batch O1 was subjected for Stability study and found stable for 1 month. Hence, O1 batch was the optimized batch.

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