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DEVELOPMENT AND EVALUATION OF TRAMADOL HCL BI-LAYERED TABLET

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ABSTRACT

The aim of the present work was to design Bilayer tablet of Tramadol HCL for bi-phasic release. Tramadol HCl is a synthetic opioid analgesic, BCS class I drug (high solubility, high permeability). Bi-layered tablets of tramadol HCl was prepared by utilizing of macromolecules (polymers) such as HPMC K100 and Xanthan gum using HPMC K100M and Xanthan gum as rate retarding polymer in sustained release layer and cross carmellose sodium as super disintigrants in immediate release layer. Nine formulations were developed and were checked using pharmacopoeial tests. The results showed that all the batches were within the standard limits. The dissolution parameters of all formulations were subjected to kinetic fitting and various statistical parameters were determined. Formulation F3, containing 34.14 mg of HPMC K100 and 10 mg of Xanthan gum produced desirable release characteristics. The best formulation (F3) follows first order, Higuchi's kinetics and non-Fickian diffusion order kinetics. F3 may be administered for the effective management to relieve moderate to moderately severe pain, including pain after surgery.

KEYWORDS: Tramadol HCl, sustained release tablet, HPMC K100, Xanthan gum and, zero order kinetics, non-Fickian diffusion mechanism.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs. The goal of any drug delivery system is to provide a therapeutic amount of the drug at

the site an effective throughout the entire duration of therapy and then maintain the desired drug concentration.[1]

Generally, conventional extended dosage forms delay the release of therapeutic systemic levels and do not provide a rapid onset of action. Immediate release DDS are intended to disintegrate rapidly and exhibit instant drug release. They are associated with a fast increase and decrease and hence fluctuations in drug plasma levels which leads to reduction or loss in drug effectiveness or increased incidence of side effects.[2] Administration of the DDS several times per day is therefore necessary to compensate the decrease in drug plasma concentration due to metabolism and excretion. In many therapies, extended-release preparations are considered desirable but for many drugs, significant daily variations in pharmacokinetics and/or drug effects have been demonstrated on human beings. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve, especially for once-daily dosage forms, partly because the environment for drug diffusion and absorption varies along the gastrointestinal (GI) tract.[3]

On the basis of these considerations, a new oral delivery device was proposed, in the form of a double-component tablet, one portion is formulated to obtain a prompt release of the drug with the aim of reaching a high serum concentration in a short period of time. The second portion is a prolonged-release layer which is designed to maintain an effective plasma level for a prolonged period of time. The pharmacokinetic advantage relies on the fact that drug release from fast releasing component leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining layer.[4,5]

Bilayer tablet is new concept for successful development of sustained release formulation along with various features to provide a way of successful drug delivery system that include an immediate release (IR) layer and an Sustained release (SR) layer.[6]

Need of bi-layered tablet

For the administration of fixed dose combinations of different APIs, prolong the drug product life cycle, buccal/mucoadhesive delivery systems; fabricate novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery.[7]

Controlling the delivery rate of either single or two different active pharmaceutical ingredients.[8]

To modify the total surface area available for API layer either by sandwiching with one or two in active layers in order to achieve swellable/erodible barriers for modified release.

To separate incompatible Active pharmaceutical ingredient (APIs) from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property).[9]

Advantages of bi-layered tablet dosage form[10, 11,12]

1. Bilayer tablets can be designed in such manner as to modify release as either of the layers can be kept as extended and the other as immediate release.
2. Bi-layer tablet is suitable for preventing direct contact of two drugs and thus to maximize the efficacy of combination of two drugs.
3. Separation of incompatible components.
4. Greatest chemical and microbial stability over all oral dosage form.
5. Objectionable odor and bitter taste can be masked by coating technique.

Disadvantages of bi-layered tablet dosage form[13]

1. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
2. Difficult to swallow in case of children and unconscious patients.
3. Adds complexity and bilayer rotary presses are expensive.

Types of bi-layered tablet dosage form[14]

1. Homogenous type

Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner.

2. Heterogeneous type

Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances.

VARIOUS TECHNIQUES FOR PREPARATION OF BILAYER TABLETS

- OROS® push pull technology[15]
- L-OROS tm technology[16]
- EN SO TROL technology[17]
- DUROS technology[18]
- Elandrug.technologies Dual release drug delivery system.[19]
- PRODAS technology[20]
- GEMINEX technology[21]

MATERIALS AND METHODOLOGY

Tramadol HCL, obtained from Virdev Intermediates Pvt.Ltd, Crosscarmellose, HPMC K1oo, Xanthun Gum, PVP K30, Lactose, Aerosil, Talc, Magnesium Strearate, Isopropyl Alcohol, Potassium dihydrogen orthophosphate, Sodium hydroxide, obtained from SD Fine, Mumbai.

PREFORMULATION STUDIES

Preformulation testing is the first step in the rational development of dosage forms of the drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass-produced. A thorough understanding of physicochemical properties may ultimately provide a rational for formulation design or support the need for molecular modification or merely confirm that there are no significant barriers to the compounds development. The goals of the program therefore are.

- To establishment the necessary physicochemical characteristic of a new drug substance.
- To determine its kinetic release rate profiles.
- To establish its compatibility with different excipients.

Hence, preformulation studies on the obtained sample of drug include physical tests and compatibility studies.

Determination of melting point[22]

Melting point of Tramadol HCl was determined by digital melting point apparatus. In this method the capillary tube was sealed with gentle heating from one end. Then the small quantity of pure drug Tramadol HCl was filled into the sealed capillary tube. Capillary tube was inserted into to the tube which was dipped in mineral oil phase. Gently the oil bath was

heated, as soon as the powder had started melting the heating was stopped and the temperature was noted down.

Drug-Excipient Compatibility study: Fourier Transform Infra-Red spectroscopy (FT-IR)[23]

FTIR spectra help to confirm the identity of drug and to detect the interaction of the drug with the carriers. IR spectroscopy of pure drug and physical mixture of drug with polymers was carried out using Shimadzu FTIR to check the compatibility between drug and polymers. The IR spectra of drug with polymers were compared with the standard IR spectrum of the pure drug.

In this study, pelletization of potassium bromide (KBr pellets) was employed. Before forming the pellet of potassium bromide, it was completely dried at 100^{o}C for one hour and after drying it was thoroughly mixed with the sample in the ratio 1 part of drug and 100 part of KBr. The mixture was compressed to form a disc using the dies. This disc was placed in the sample chamber and a spectrum was obtained which was further subjected to interpretation.

Differential Scanning Calorimeter (DSC)[24]

DSC (Perkin-Elmer thermal analysis) studies were carried out in order to characterize the physical state of drugs. Sample of pure drug and physical mixture were placed in the aluminium pans and thematically sealed. The heating rate was 10^{o}C per min using nitrogen as pure gas. The DSC instrument was calibrated for temperature using indium. In addition, the enthalpy calibration indium was sealed in aluminum pan with sealed empty pans as reference.

Preparation of reagents[25]

- **0.2M KCl solution**: 14.91g of KCl dissolved in 1000ml distilled water.
- **0.2M HCl solution:** 17ml HCl dissolved in 1000ml distilled water.
- **0.2M Potassium dihydrogen ortho-phosphate:** 6.085g of KH2PO4 in 250ml distilled water.
- **0.2M Sodium hydroxide:** 2g of NaOH dissolve in 250ml distilled water.

Preparation of pH 1.2 buffer

50ml of 0.2M KCl solution taken in 200ml volumetric flask and 85ml of 0.2M HCl added and then made up the volume up to 200ml with distilled water.

Preparation of pH 7.4 phosphate buffer

Take out accurate volume of NaOH. I.e. 195.5ml and mixed it into 250ml potassium dihydrogen phosphate solution. The volume was made up to 1000ml with distilled water.

Analytical Method

Determination of analytical wavelength of Tramadol HCl[26]

Most of the drugs absorbs light UV wavelength (200-400nm), since generally they aromatic contain double bond. The UV spectrophotometric method was selected in the present study for the estimation of Tramadol HCl. The drug solution was scanned in between the wavelength of 200-400nm.

Standard graph of Tramadol hydrochloride in pH 1.2 buffer and pH 7.4 Phosphate buffer

Standard solution: 100mg of Tramadol HCl was weighed and dissolved in 100ml of buffer and the final volume was made up to100ml with buffer (pH 1.2 and 7.4) to give a concentration of 1mg/ml (1000µg/ml) respectively.

Stock solution: From the standard solution, II stock solution was prepared by diluting 25ml of above solution to 100ml with pH1.2 buffer and pH7.4 buffer (250µg/ml) separately. From this II stock solution 25, 50, 75, 100, 125 and 150mg/ml dilutions were prepared by diluting 1,2,3,4,5 and 6ml to 10ml with pH1.2 and 7.4 buffer solution. The absorbance of each sample was measured using UV spectrophotometer against pH1.2 and pH7.4 phosphate buffer as blank.

Formulation of bilayer tablet of Tramadol HCl[27]

Tramadol HCl and various polymers viz, crosscarmellose, HPMC-K-100M, xanthun gum, lactose, aerosil were weighed accurately and were passed through # 30 sieve (Individually). All the ingredients for immediate release given in Table 1 and sustained release formula given in Table 2 were mixed separately using motor and pestle for 15 min. Required quantity of PVP K30 was added to Isopropyl alcohol with constant stirring to form a clear solution. Binder solution was added to sustained release material with uniform mixing to achieve end point (that is until the dump mass does not adheres). Damp mass thus obtained were passed through # 10 sieve and dried at 45^0C for 1hr. in hot air oven. Granules obtained were passed through # 20 sieve to get granules which are suitable for compression. The prepared granules were lubricated with magnesium stearate and talc. The bilayer tablet were firstly compressed

using rotary tablet press for sustained release layer and then again compressed with immediate release layer over the sustained release layer.

Evaluation of powder blends[28,29]

Bulk Density

It is the ratio of total mass of powder to the bulk volume of powder. Bulk density of all batches of Granules was determined by pouring gently 2 g of sample through a glass funnel into a 10 ml graduated cylinder. The volume occupied by the sample was recorded.

Tapped Density

Accurately weighed 5 g of the granules was placed in a 10 ml graduated measuring cylinder. Initial volume was observed. The cylinder was tapped initially 200 times from a distance of 14±2 mm. The tapped volume was measured to the nearest graduated unit. Again the tap volume was measured to the nearest graduated unit.

Carr's consolidation index

The % compressibility of the powder was direct measure of the potential powder arch or bridge strength and stability.

Hausner's Ratio

It provides an indication of the degree of densification which could result from vibration of feed hopper. Lower the Hausner's ratio better is the flowability.

Angle of repose

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane.

Compression of bi-layered tablets

The bilayer tablet of Tramadol HCl was prepared using a Rotary Mini tablet press (Shakthi Pvt. Ltd., India) equipped with flat punches. The die was initially filled with the weighed amount sustained release portion and was lightly compressed. Over this compressed layer, the required quantity of the immediate release layer powder mixture was placed and compressed to obtain hardness of the tablet 4–6 kg/cm^2. It was observed that tablet compressed at this force did not show any layer separation. The total weight of the tablet was kept constant, i.e., 350 mg for all formulation.

Evaluation of bilayer tablets[30]

General Appearance

The control of a general appearance of a tablet involves the measurement of a number of attributes such as a tablet's size, shape, color.

Immediate release layer: - white color

Sustained release layer: - Yellow color

Thickness

The homogeneity of tablet size required a certain thickness of tablet. Digital screw gauze was used to determine thickness.

Hardness[31]

In this five tablets were selected randomly and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2.

Friability test[32]

Friability test was carried out to evaluate the hardness and stability instantly. In roche friabilator. 10 tablets were weighed (W_0) initially and put in a tumbling and rotating apparatus drum. Then they were subjected for completion of 4 min or 100 rpm, the tablets were again weighed. The % loss in weight or friability (F) was calculated by the formula given below.

$$\% \text{ Friability} = \frac{(\text{Initial weight of tablets} - \text{Final weight of tablets})}{\text{Initial weight of tablets}} \times 100$$

Weight variation

This test was performed to maintain the uniformity of weight of each tablet, which should be in the prescribed range. This was done by weighing 10 tablets at random and average weight was calculated. Not more than two of individual weight deviates from the average weight. The weight data from the tablets were analyzed for sample mean and percent deviation. IP limit for weight variation in case of tablets weighing 130 - 324 mg ± 7.5 % and more than 324 mg ± 5%.

Uniformity of drug content

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. The content uniformity

was mandatory for tablets. This test was performed by taking five tablets were selected randomly, weighed and powdered. A tablet triturate equivalent to 100mg of drug weighed accurately, dissolved in 10 ml of methanol and diluted to 100ml with buffer (PH 1.2 and 7.4). Further dilutions were done suitably and absorbance was measured at 271nm using UV spectrophotometer.

In-Vitro Dissolution Studies[33]

The dissolution property of the prepared tablets was determined using USP dissolution testing apparatus I (Paddle type). The dissolution test was performed using 900 ml of pH 1.2 acid buffer for first 2 hrs and pH 7.4 phosphate buffer for 10 hrs. at 37 ± 0.5°C and 50 rpm. The height of paddle was adjusted at about 2.5cm above the surface of tablet. Samples were replaced by its equivalent volume of dissolution medium. The samples were filtered through Whatman filter paper (no.41) and solutions were analyzed using UV spectrophotometer after suitable dilution.

Kinetic analysis of dissolution data

The results of *in vitro* release profiles obtained for all the formulations were fitted into four models of data treatment as follows.

1. Cumulative percent drug released versus time (zero-order kinetic model).
2. Log cumulative percent drug remaining versus time. (First-order kinetic model).
3. Cumulative percent drug released versus square root of time (Higuchi's model).
4. Log cumulative percent drug released versus log time (Korsmeyer-Peppas equation).
5. Cubic root of cumulative percent drug released versus time (Hixson and Crowell's cubic root).

Zero Order Kinetics

It describes the system in which the drug release rate is independent of its concentration. A zero-order release would be predicted by the following equation.

$$\mathbf{A_t = A_0 - K_0 t}$$

Where:

A_t = Drug release at time 't'

A_0 = Initial drug concentration

K_0 = Zero-order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0.

Cumulative percent drug released versus time

First Order Kinetics

It describes the drug release from the systems in which the release rate is concentration dependent. A first-order release would be predicted by the following equation

$$\text{Log } C = \text{Log } C_o - \frac{Kt}{2.303}$$

Where:

C = Amount of drug remained at time‘t’

C_0 = Initial amount of drug

K = First-order rate constant (hr^{-1}).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follows First-order kinetics. The constant ‘K’ can be obtained by multiplying 2.303 with slope values.

Higuchi’s Model

Drug released from the matrix devices by diffusion has been described by following Higuchi’s classical diffusion equation.

$$Q = \left(\frac{D\varepsilon}{\tau}(2A - \varepsilon C_s)C_s t\right)^{1/2}$$

Where,

Q = Amount of drug released at time‘t’

D = Diffusion coefficient of the drug in the matrix

A = Total amount of drug in unit volume of matrix

C_S = The solubility of the drug in the diffusion medium

ε = Porosity of the matrix

τ = Tortuosity

t = Time (hrs) at which ‘Q’ amount of drug is released.

Equation may be simplified if one assumes that D, C_s and A are constant.

Then equation becomes.

$$\mathbf{Q = Kt^{½}}$$

When the data is plotted according to equation-4 i.e., cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

Korsmeyer-Peppas model (Power Law)

The power law describes the drug release from the polymeric system in which release deviates from Fickian diffusion, as expressed in following equation.

$M_t / M_\infty = ktn$

$\log [M_t / M_\infty] = \log k + n \log t$

Where,

M_t and M_∞ are cumulative amounts of drug release at time t and infinite time

k=constant incorporating structural and geometrical characteristics of CR device,

n= diffusional release exponent indicative of the mechanism of drug release for drug dissolution.

To characterize the release mechanism, the dissolution data $\{M_t / M_\infty < 0.6\}$ are evaluated.

A plot of **$\log \{M_t / M_\infty\}$ versus log t** will be linear with **slope of n and intercept gives the value of log k**.

Antilog of log k gives the value of k. Peppas used the **n value** in order to characterize different release mechanisms.

Hixson and Crowell's cubic root law of dissolution

The Noyes-Whitney's equation assumes that surface area of the dissolving solid remains constant during dissolution, which is practically not possible for dissolving particles. Hence, dissolution methods that involve use of constant surface area discs are employed to determine the rate of dissolution.

To account for the particle size decrease and change in surface area accompanying dissolution, Hixson and Crowell's cubic root law of dissolution is used.

$W_0^{1/3} - W^{1/3} = Kt$

Stability Studies

Stability of a dosage form has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specification.

Objective of the study

The purpose of stability studies is to provide evidence that the quality of drug substance or drug product varies with time under the influence of a verity of environmental factors such as temperature, humidity and light enables recommended storage conditions, re-testing periods and shelf-lives to be established. Accelerated stability study was carried out as per the ICH guidelines.

Procedure

In the present study, the stability studies were carried out for a specific time up to 90 days for selected formulations. The selected formulation were analyzed for the physical appearance and drug content.

Stability Studies

Stability of a dosage form has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specification.

Table no 1: Composition of immediate release layer of Tramadol Hydrochloride.

Ingredients	Quantity per tablet(mg)
Tramadol HCl	25
Lactose monohydrate	90
Crosscarmellose	2
PVP K30	10
Aerosil	19
Magnesium stearate	2
Talc	2

Table no 2: Composition of Sustained release layer of Tramadol Hydrochloride.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tramadol Hcl	75	75	75	75	75	75	75	75	75
Lactose monohydrate	82.58	90.5	61.36	75.5	68.43	70.5	80.5	60.5	89.64
Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Xanthan gum	2.92	5	10	10	17.07	5	15	15	10
HPMC K100	20	10	34.14	20	20	30	10	30	5.86
PVP K30	9	9	9	9	9	9	9	9	9
Isopropyl alcohol	QS	QS	QS	QS	QS	QS	QS	QS	QS
Magnesium stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Talc	3	3	3	3	3	3	3	3	3
Tartrazine	15.5	1.5	1.5	1.5	1.3	1.3	1.3	1.3	1.3

*All the quantities are in mg/tablet

RESULTS AND DISCUSSION

A successful attempt was made to formulate Tramadol HCL bilayer tablets using crosscarmellose as immediate release polymer and HPMC K-100 and Xanthan gum as release retardants using wet granulation method. Total nine formulations were prepared, composition of each formulation is shown in table no:1 and 2. The formulated tablets were characterized for various physicochemical parameters.

Melting point of Tramadol HCl

The melting point of Tramadol HCl was determined by capillary method using digital melting point apparatus (in triplicate) and found to be 180^0 **C** which is within the reported melting point range of 180-181°C. Thus obtained melting point was in agreement with literature melting point which confirms the purity of drug.

ANALYTICAL METHODS

- **Determination of λ max**

The absorption maximum of the standard solution was scanned between 200-400 nm regions on UV-visible spectrophotometer (Shimadzu UV-Vis 1700). The wavelength of maximum absorbance (λ max) was found to be 272 nm in both pH 1.2 buffer and pH 7.4 buffer. The curve was found to be linear in the range of 25-150µg/ml with regression value of 0.999 and 0.999 respectively.

Fourier transport infrared spectroscopy (FTIR)

Infrared spectroscopic, analysis for drug alone and in combinations with other excipients were carried out. The spectrum for the pure drug showed the following functional group at their respective frequency as shown in table no: 3and figure no :1,2

The IR spectra of the pure drug was compared with the characteristic peak of prepared granules and the spectra was found be super imposable to that of the pure drug. There are no other peaks which give evidence that there was no drug polymer interaction. These indicate that drug is compatible with formulation components.

Differential Scanning Calorimetry (DSC) Analysis

DSC is useful in the in the investigation of solid state interactions. The DSC pattern of pure Tramadol HCl and prepared drug with immediate release and sustained release granules are shown in figure 3,4,5 respectively. Pure Tramadol HCl showed a sharp endothermic peck at

200.62°C which corresponding to its melting point. There was no negligible change in the melting endotherm of the physical mixture in immediate release (195.92) and sustained release granules (196.15) compared to pure drug.

This observation further supports the IR spectroscopic results which indicated the absence of any interaction between the drug and additives used in the preparations.

EVALUATION PARAMETERS

Pre-compressional parameters: In the present work an attempt has been made to prepared tramadol bi-layered tablets using HPMC K100M and xanthan gum for sustained release and crosscaramellose sodium for immediate release phase.

Blended drug polymer mixture of all the formulation were subjected for various Precompressional evaluations such as.

Bulk density: Bulk density depends upon particle size, shape, and tendency of particles to adhere together. The values of bulk density were found to range from 0.381±0.003 to 0.411±0.005.

Tapped density: The values of tapped density were found to range from 0.455±0.006 to 0.485±0.005.

Carr's consolidation index: The results of the Carr's consolidation index of all the formulations ranges from 14.83±1.260 to 16.56±0.840.

Hausner's ratio: It was ranging from1.17±0.015 to 1.19±0.011. Lower the Hausner's ratio better is the flowability, i.e., all the preparation showed that they had good flow properties.

Angle of repose (θ): All the formulations showed angle of repose value in the range of 23.74±0.960 to 25.00±1.433. The angle of repose value (< 30) indicated good flow properties. The values indicated that all the formulation showed acceptable flow properties with low standard deviation value.

POST COMPRESSION PARAMETERS

Nine formulations of Tramadol with HPMCK100M, xanthan gum and mixture of HPMCK100M and Xanthan gum in different concentration were prepared. All the formulation batches were prepared by wet granulation technique.

Thickness

The thickness of the tablet is reported in the micrometer (mm). The thickness of tablet indicates that, die fill was uniform. The thickness depends on the size of punches and the weight of one tablet (350 mg). The value of thickness ranges between 3.25±0.009 to 3.32±0.009 mm.

Hardness

Hardness of all tablets was maintained within 4 to 6 kg/cm^2. The mean hardness values were measured for all the formulation using Monsanto hardness tester. The hardness value ranges from 5.03±0.142 to 5.36±0.251 kg/cm^2. The hardness of all formulations was almost uniform in specific method and possesses good mechanical strength.

Friability (F)

Another measure of tablet strength is friability. The % friability for all the formulations was below 1% indicating that the friability was within the prescribed limits the results of friability test indicates that the tablet possesses good mechanical strength.

Weight Uniformity

All the tablets were passed weight variation test as the average weight variation was within the Pharmacopoeial limit ±5%. The weight of all the tablets was found to be uniform with low standard deviation value.

Uniformity of drug content

The % drug content of Tramadol HCL in all the formulated tablets were found within the limits. % drug content value of Tramadol HCL was within 97.51±2.919 to 99.92±2.775% in both pH 1.2 buffer and pH 7.2 buffer. The results within the range indicate uniform mixing of drug.

***In-Vitro* Dissolution Study**

In-vitro dissolution studies of all the formulations were carried out in pH 1.2 buffer for 2 hr. and followed by pH 7.4 buffer for 10 hrs. The study was performed for 12 hr. and cumulative drug release was calculated at different time. The cumulative % drug release profiles for the formulations (F1 to F9) were tabulated in table no.4. The plot of cumulative % drug release v/s time for all formulations were plotted and depicted in figure 6.

The result revealed that the release rate of drug was inversely proportional to the quantity of polymers. Formulation coded F3 containing 34.14 mg of HPMC K100 and 10 mg of Xanthan gum produced desirable release characteristics (t50%=2.025 h, t75%=5.040 h, t90%=10.045 h), which was probably due to variation in the viscosity of the polymer matrix. An increase in the viscosity of the stagnant layer results in a corresponding decrease in drug release (due to thicker gel layer formation).

Drug Release Kinetics

To know the mechanism of drug release from this formulation the *in vitro* release data were subjected to zero order, first order, higuchi, Korsmeyer-peppas model and Hixson Crowell cube root. As clearly indicated in figure 6 the formulation did not follow a zero order release pattern. The release rate kinetic data for all other equation can seen in table5.

When the data were plotted according to the first order equation, the formulation showed a fair linearity, with regression value 0.8753 to 0.9952. Release of drug from bi-layered tablet containing polymers generally involves factor of diffusion.

In our experiments, the *in vitro* release profile drug from all the formulations could be best expressed by higuchi's equation as the plot showed high linearity (r^2=0.9841-0.9971).

To conform the diffusion mechanism the data was fitted in to Korsmeyer et al., equation all the formulation showed good linearity with slope (n values ranging from 0.6172 to 0.7010) which indicating that analomus diffusion mechanism.

Stability Studies

Short-term accelerated stability study was performed on the promising formulations F3 by storing the samples at 40±2ºC with 75±2 RH for 90 days. The samples were tested for any changes in physical appearance and drug content studies at monthly intervals.

Table no 3: Major peaks of Tramadol HCl in IR spectra.

Sample code	NH stretching	OH stretching	CH Aromatic stretching	NH bending	C=C Aromatic Stretching	C-N stretching
Pure drug	3342.10	3308.70	2974.33	1606.7	1577.80	1288.49
Physical mixture of drug and polymer	3300.10	3318.11	2920.97	1603.73	1577.80	1288.40

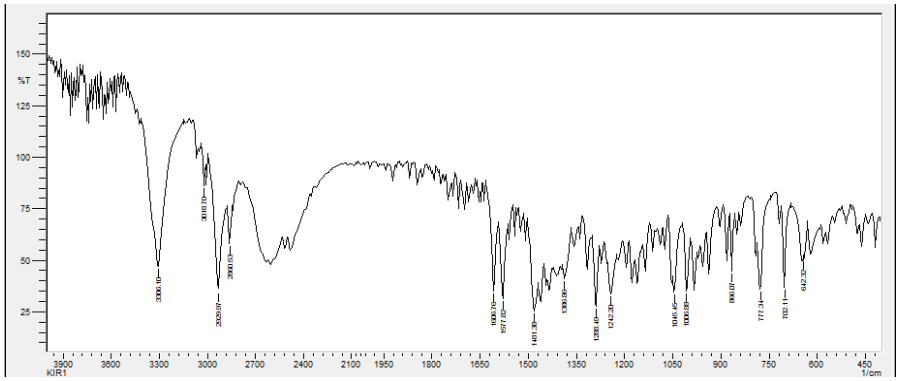

Figure no 1: FT-IR of Tramadol HCl.

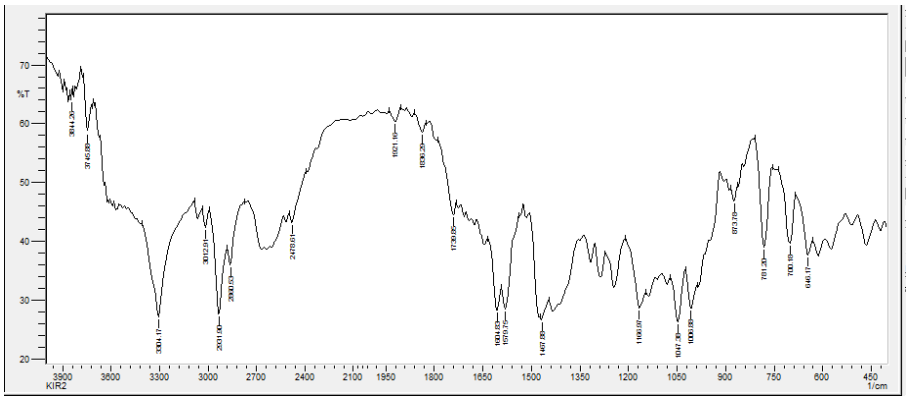

Figure no 2: FT-IR Spectra of physical mixture of Drug + polymers.

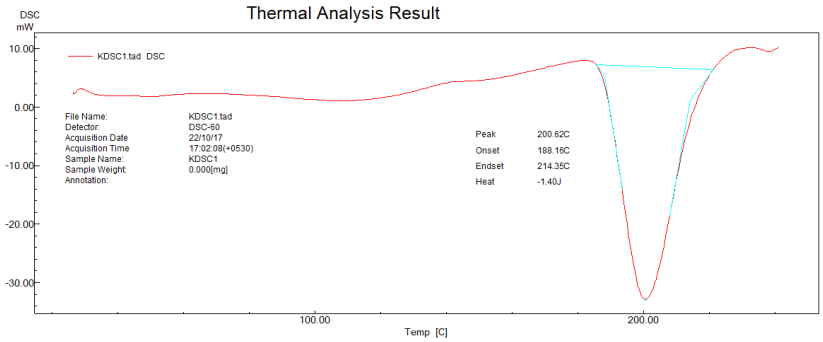

Figure no 3: DSC of Tramadol HCl.

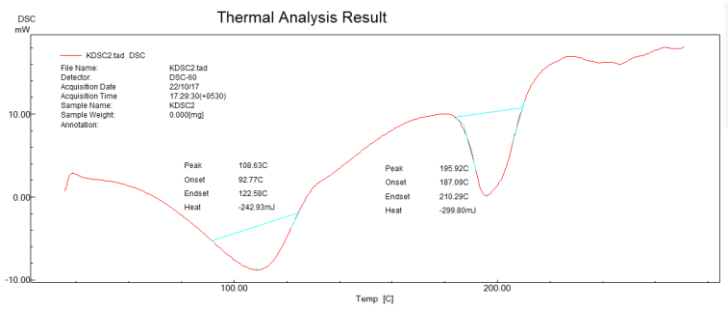

Figure no 4: DSC of physical mixture of Drug in immediate release granules.

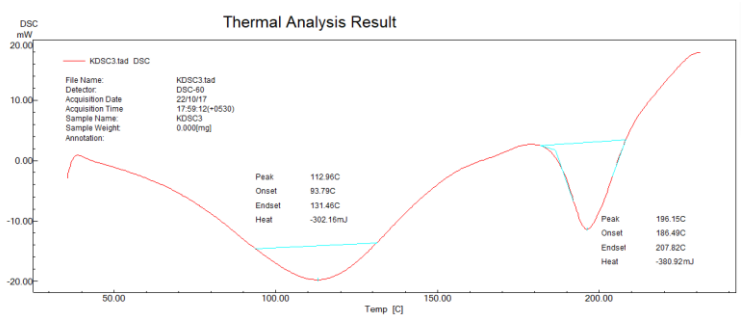

Figure no 5: DSC of physical mixture of Drug in sustained release granules.

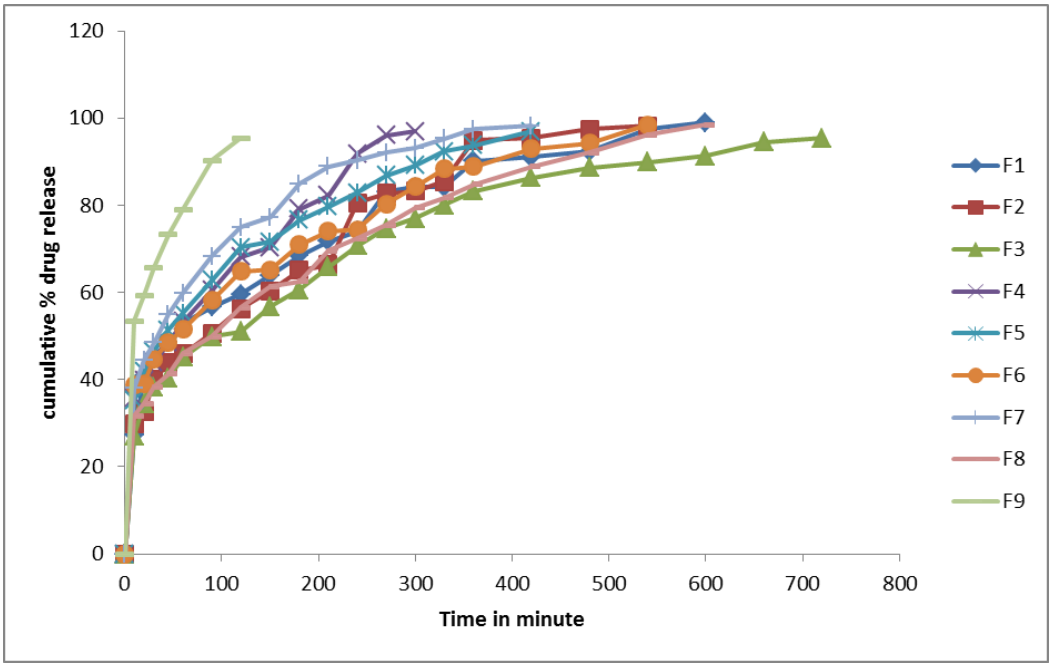

Figure no. 6: *In vitro* dissolution profile of F1 to F9 formulation.

CONCLUSION

Form the present study the following conclusion can be drawn.

Bi-layered tablets of tramadol HCl was prepared by utilizing of macromolecules (polymers) such as HPMC K100 and Xanthan gum using HPMC K100M and Xanthun gum as rate retarding polymer in sustained release layer and crosscarmellose as super disintigrants in immediate release layer. The results revealed that the amount of polymers was inversely proportional to the rate of drug release from the formulation. Utilization of polymers in the formulation was beneficial for obtaining prolonged release of the active moiety. Formulation F3 follows first order release and a non-Fickian diffusion mechanism. F3 may be administered for the effective management **to relieve moderate to moderately severe pain, including pain after surgery**. The best formulation shows good retaining characteristics. It

also reduces the frequency of administration, which will ultimately improve the clinical response.

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