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Research Article

Formulation and Evaluation of Tramadol Hydrochloride Sustained Release Matrix Tablets

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ABSTRACT

The ultimate goal of any oral drug delivery system is the successful delivery of the drug, in which almost 90% of the drugs are administered to the body for the treatment of various disorders and diseases as it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. The aim of the present study is to formulate sustained release matrix tablets of a model drug (Tramadol hydrochloride) using HPMC 100 MCR, HPC and EC 7cps as rate retarding polymers, microcrystalline cellulose as bulking agent, magnesium stearate as lubricant and aerosil as glidant. Drug and polymer interactions were evaluated by using FTIR and DSC. The FTIR spectrum and DSC thermograms stated that drug and polymer are compatible to each other. Tablets were prepared by direct compression technique. The micromeritic properties of formulation mixtures of all the formulations were carried out and they were found to be as angle of repose (31.15^0- 40.10^0), bulk density (0.310g/ml-0.337g/ml), tapped density (0.355g/ml-0.59g/ml), Carr's index (8.11%-15.3%), Hausner's ratio (1.08-1.18) which are within the limits. The formulated tablets were physically acceptable and exhibited acceptable weight variation, friability. *In vitro* dissolution studies were carried out using USP type-II dissolution apparatus and of all the formulations F_6 (containing HPMC and HPC in equal proportions) exhibited prolonged drug release for about 8 hrsas per the objective of the work. The percent drug content varied between 88% to 99%. It can be concluded from the study that the sustained release tablets can be better alternative over immediate release tablets by improving patient compliance and reducing frequency.

Keywords: Sustained release, Matrix tablets, HPMC 100 MCR, HPC, EC, Osteoarthritis.

INTRODUCTION

Sustained release drug delivery systems are developed to modulate the release of drug, in order to achieve specific clinical objectives that cannot be attained with conventional dosage forms. Possible therapeutic benefits of a properly designed SR dosage form include low cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profiles attainable, increased convenience and patient compliance. There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of the drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak and trough concentration, side effects and possibly improves the specific distribution of the drug[1].

Tramadol is a non-steroidal anti-inflammatory drug, which is used in the treatment of osteoarthritis when NSAIDs like Acetaminophen, or COX-2 inhibitors alone produce inadequate pain relief. After oral administration, Tramadol is rapidly and almost completely absorbed. Sustained-release tablets reach to peak concentrations after 4.9 hrs and have a bioavailability of 87% to 95% compared with capsules. The mean elimination half-life is ~6 hrs and requires dosing every 6 hrs in order to maintain optimal relief of chronic pain. Consequently, once-daily extended-release tablets have been formulated. Long term treatment with sustained-release tramadol once daily is generally safe in patients with osteoarthritis or refractory low back pain and is well tolerated. It has the potential to provide patients increased control over the management of their pain, fewer interruptions in sleep, and improved compliance. Tramadol, a synthetic opioid of the aminocyclohexanol group, is a centrally acting analgesic with weak opioid agonist properties. Tramadol has been proved to be effective in both experimental and clinical pair without causing serious side effects. Tramadol and its metabolites are excreted primarily in the urine with observed plasma half-lives of 6.3 and 7.4 hours for

Table 2: Calibration Table of Tramadol hydrochloride in pH 1.2 buffer.

Conc (µg/ml)	Absorbance
0	0
20	0.111
40	0.241
60	0.365
80	0.482
100	0.671

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Table 1: Formula for preparation of formulations

S.no	Ingredients	F1	F2	F3	F4	F5	F6
01.	Tramadol hydrochloride(mg)	100	100	100	100	100	100
02.	Microcrystalline cellulose(mg)	75	55	70	85	25	25
03.	Hydroxypropyl cellulose(mg)	30	45	30	-	-	60
04.	Hydroxypropylmethyl cellulose(mg)	-	-	20	30	60	60
05.	Ethyl cellulose(mg)	40	45	25	30	60	-
06.	Aerosil(mg) (1%)	2.5	2.5	2.5	2.5	2.5	2.5
07.	Magnesium stearate(mg) (1%)	2.5	2.5	2.5	2.5	2.5	2.5

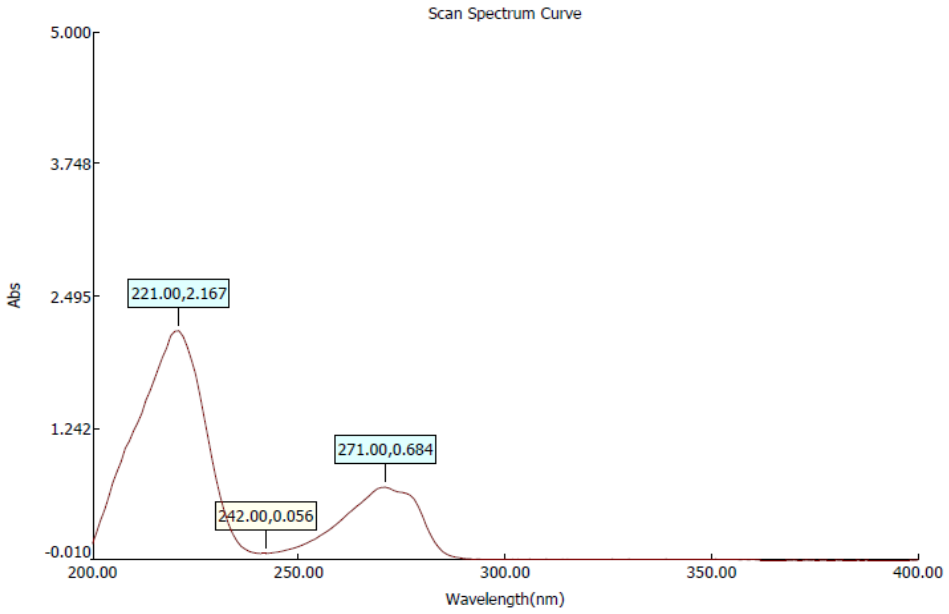

Figure 1: Spectrum of Tramadol hydrochloride in pH 1.2 buffer.

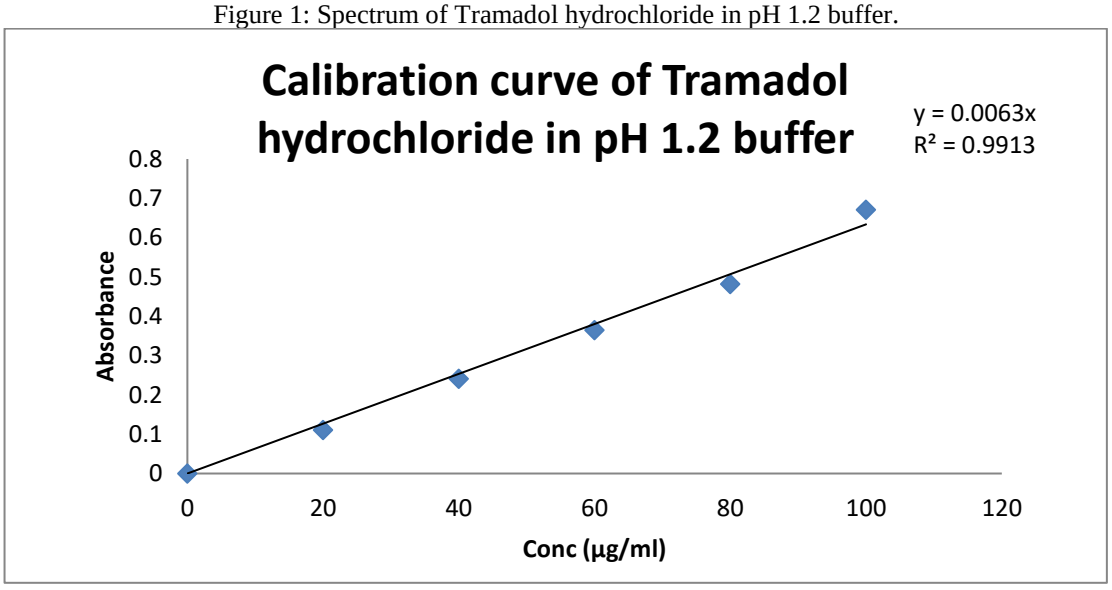

Figure 2: Standard Calibration Curve of Tramadol hydrochloride in pH 1.2 buffer.

Tramadol and M_1, respectively.

Sustained Release is achieved by either chemical modification of the drug or modifying the delivery system, e.g., use of a special coating to delay diffusion of the drug from the system. Chemical modification of drugs may alter properties such as distribution, pharmacokinetics, solubility, or antigenicity. One example of this is attachment of polymers to the drugs to lengthen their lifetime by preventing cells and enzymes from attacking the drug[2].

It is difficult to create sustained-release formulations for many hydrophobic drugs because they release too slowly

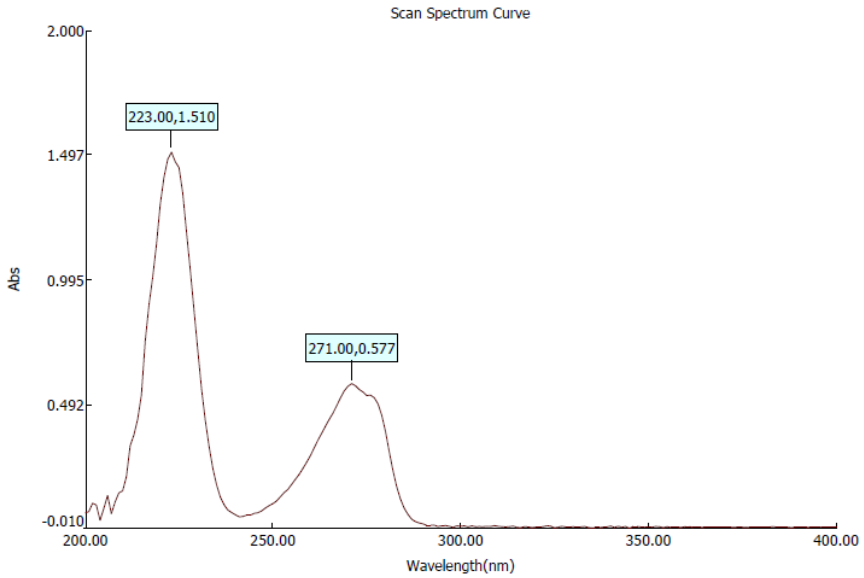

Figure 3: Spectrum of Tramadol hydrochloride in acetate buffer pH 4.5.

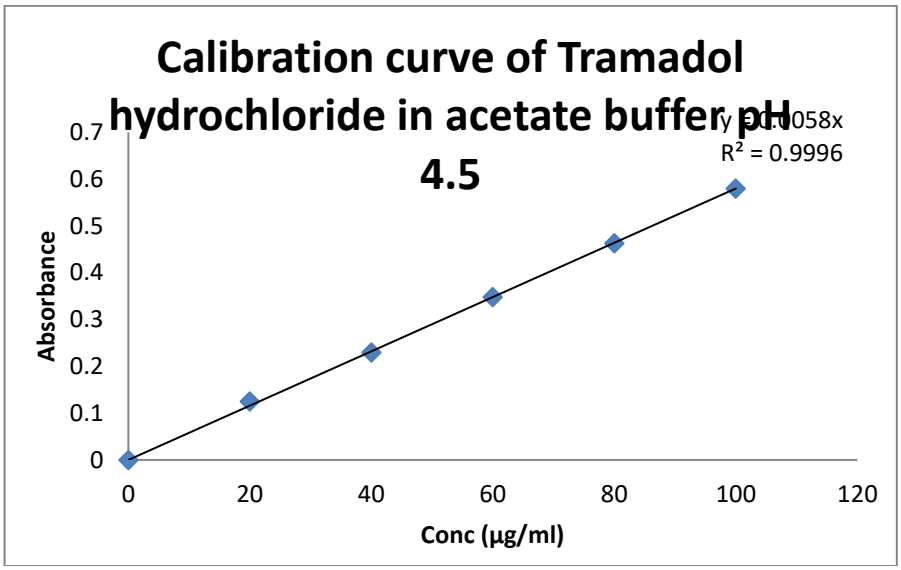

Figure 4: Standard Calibration Curve of Tramadol hydrochloride in acetate buffer pH 4.5

Table 3: Calibration Table of Tramadol hydrochloride in acetate buffer pH 4.5:

Conc (µg/ml)	Absorbance
0	0
20	0.125
40	0.230
60	0.348
80	0.463
100	0.580

from the nanoparticles used to deliver the drug, diminishing the efficacy of the delivery system.

Compliance is a big problem in medical care. Most patients do not like to take medications or fail to take them as instructed. Drugs with sustained release can remedy some of these problems. Once daily dosage with sustained action is likely to improve the compliance rate to 80% when compared with 40% for three or four times a day[3].

Ethocel (EC) has been used as a membrane substance in sustained-release beads, often in combination with other polymers, such as hydroxypropyl methyl cellulose (HPMC) and hydroxypropylcellulose (HPC)[4].

Parameters for the drug to be formulated as SR dosage form:

Physicochemical parameters:

Molecular weight < 1000 daltons

Solubility >0.1mg/ml for pH 1.0 to pH 7.8

Apparent partition coefficient high

Absorption mechanism diffusion

General absorbability from all GI segments

Release should not be influenced by pH and enzymes.

Pharmacokinetic parameters:

Elimination half life should be between 2 to 8 hours.

Total clearance should not be dose dependent

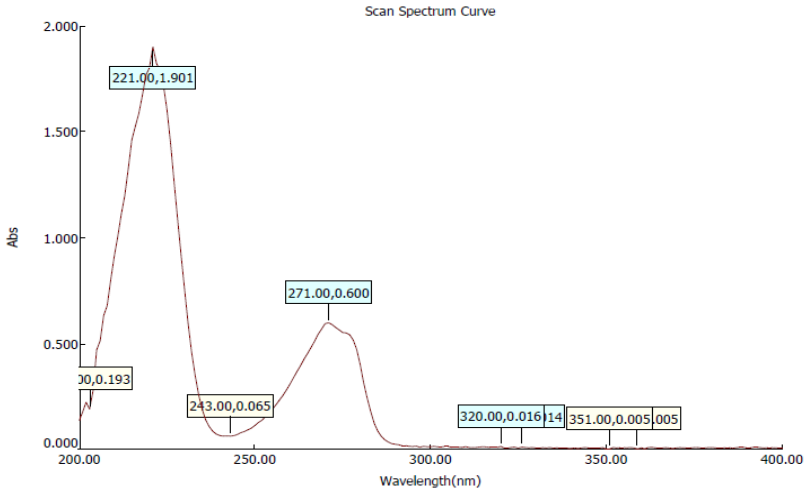

Figure 5: Spectrum of Tramadol hydrochloride in phosphate buffer pH 7.4.

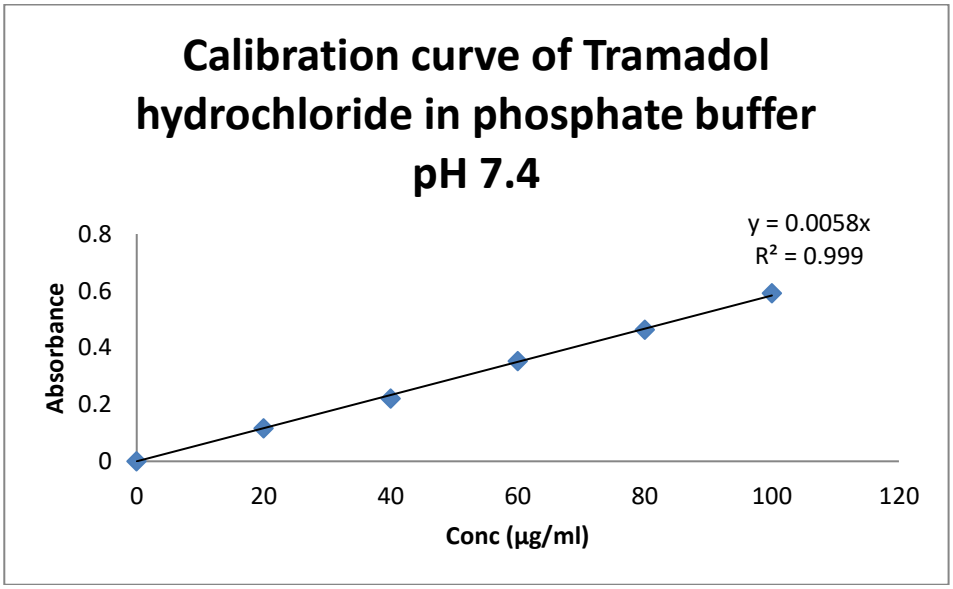

Figure 6: Standard Calibration Curve of Tramadol hydrochloride in phosphate buffer pH 7.4.

Elimination rate constant required for design
Absolute bioavailability should be 75% or more
Intrinsic absorption rate must be greater than release rate

MATERIALS AND METHODS

Materials

HPMC 100 MCR, HPC, Ethyl cellulose 7cps, Microcrystalline Cellulose, Aerosil, Magnesium Stearate, Tramadol hydrochloride, Hydrochloric acid, Sodium acetate trihydrate, Glacial acetic acid, Potassium dihydrogen orthophosphate, Sodium hydroxide, Distilled water. All the excipients, and chemicals were of analytical grade.

Pre-formulation Studies

Drug - Excipient Compatibility

Fourier Transmission Infrared Spectroscopy:

Study was carried out using FTIR (BRUKER) where the spectra of pure drug, individual excipients and physical mixtures of formulation were taken. The specific peaks of drug and the polymers were studied for the interactions.

Differential Scanning Calorimetry:

DSC studies were performed using a UNIVERSAL V4.5A TA INSTRUMENTS. Accurately weighed samples (about 3 mg) were placed in a sealed aluminium pan, before heating under nitrogen flow (20 ml/min) at a scanning rate 20^0C/min from 40 to 300^0C. An empty aluminium pan was used as reference. DSC thermograms of pure drug substance and their physical mixtures were recorded.

Determination of maximum wavelength λ_{max}:

Maximum wavelength λ_{max} was determined in all the three buffers used i.e., pH 1.2 buffer, acetate buffer pH 4.5 and phosphate buffer pH 7.4. Standard stock solution was prepared by dissolving 10mg Tramadol hydrochloride in 10ml buffer resulting in 1mg/ml concentration. From the stock, working standard was made by taking 1ml and making up to 10ml using buffer resulting 100µg/ml concentration solution. These solutions were scanned from 200-400 nm to determine to maximum wavelength λ_{max} using UV-Visible spectrophotometer.

Calibration

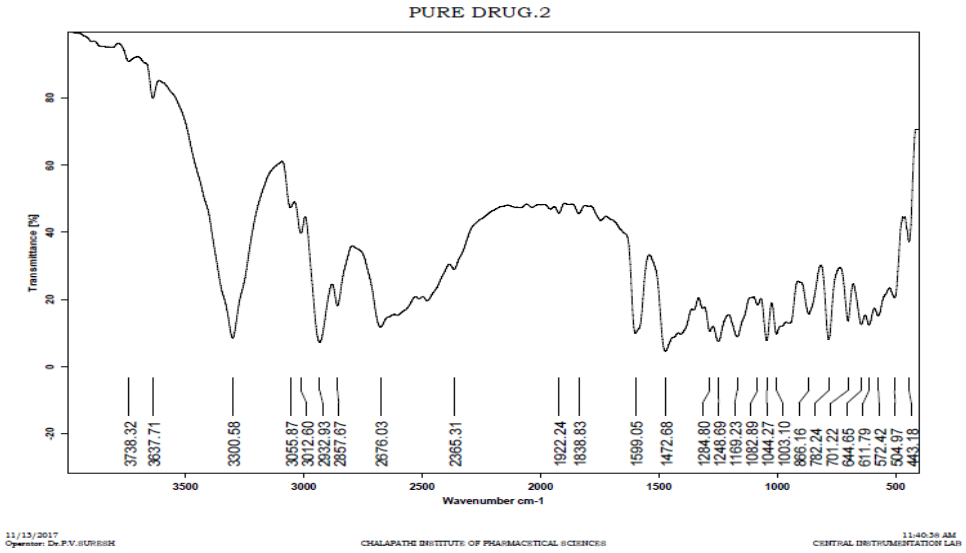

Figure 7: FTIR spectrum of pure Tramadol hydrochloride.

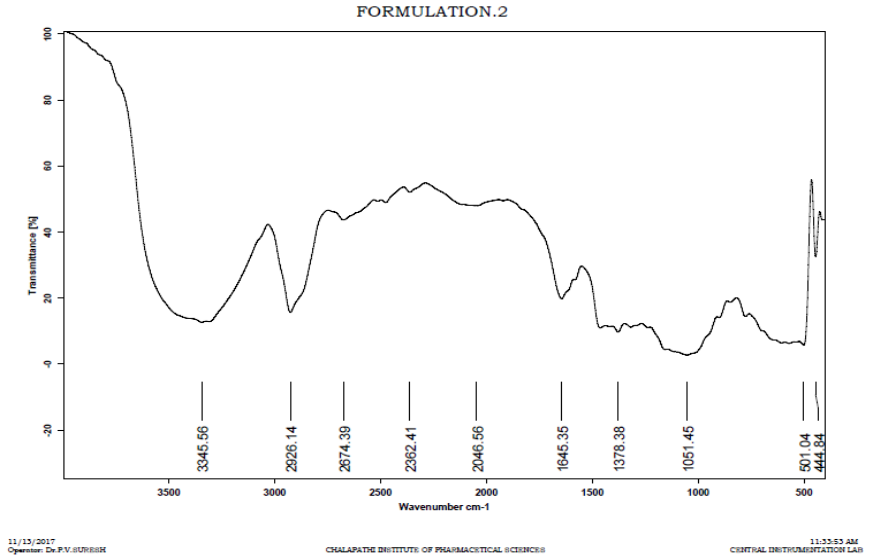

Figure 8: FTIR spectrum of best formulation.

Table 4: Calibration Table of Tramadol hydrochloride in phosphate buffer pH 7.4:

Conc (µg/ml)	Absorbance
0	0
20	0.116
40	0.220
60	0.352
80	0.463
100	0.591

Standard stock solution was prepared by dissolving 10mg Tramadol hydrochloride in 10ml buffer resulting in 1mg/ml concentration. From the stock, 0.2ml (20µg/ml), 0.4ml (40µg/ml), 0.6ml (60µg/ml), 0.8ml (80µg/ml) and 1ml (100µg/ml) were transferred into 10 ml volumetric flasks and the volume was made up to 10 ml with buffer. The resulting working standard solutions absorbance was measured at its maximum wavelength and calibration curve was constructed. The same procedure was followed for all the three buffers i.e., pH 1.2 buffer, acetate buffer pH 4.5 and phosphate buffer pH 7.4.

Formulation

Tablets were prepared by direct compression method. Formulations were made using different combinations of the polymers at different ratios within the range of 8-30% in order to know about drug release pattern.

Required quantities of the ingredients were weighed, transferred into mortar and triturated in order to make the drug to be uniformly distributed within physical mixture. The powder blend was weighed and compressed using 8mm die in tablet compression machine and the tablets were made.

Evaluation

Pre-Compression Parameters

Bulk density (D_b)

The bulk density depends on particle size distribution,

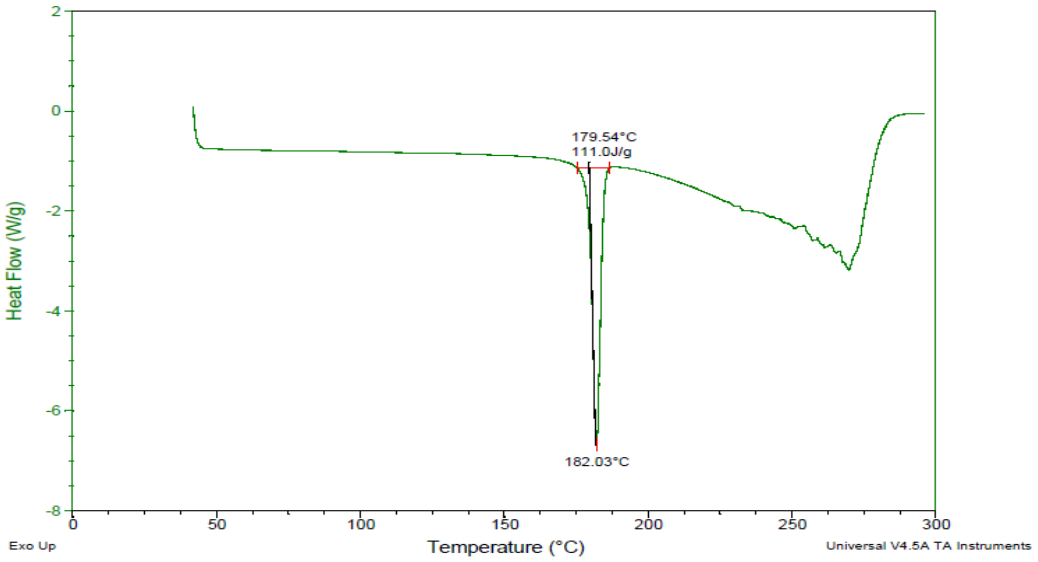

Figure 9: DSC Thermogram of pure drug.

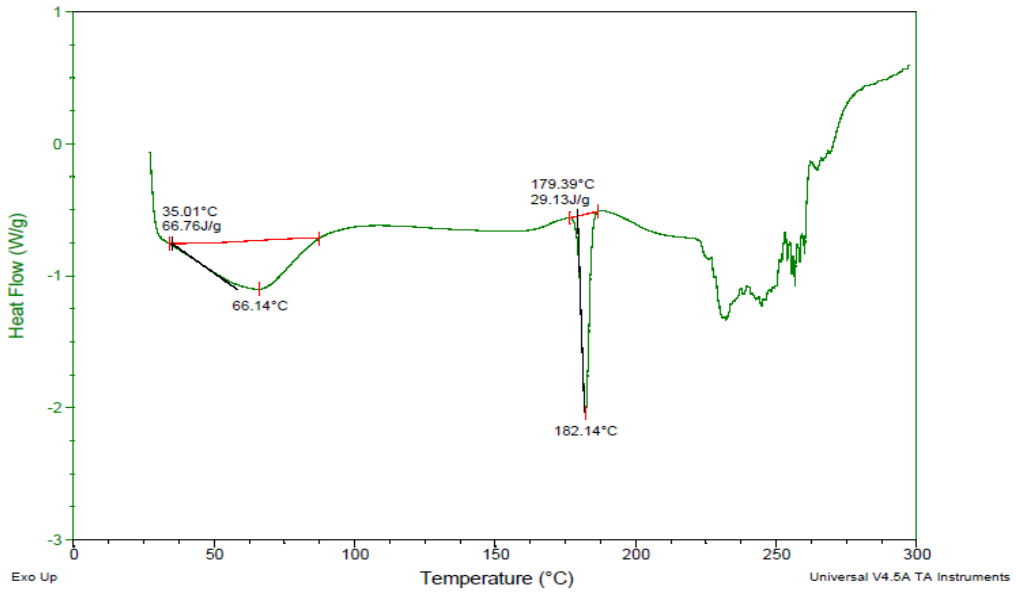

Figure 10: DSC Thermogram of best formulation.

shape and cohesiveness of particles. Accurately weighed quantity of powder (m) was carefully poured into the graduated cylinder and volume (V_0) was measured. The bulk density was calculated by using formula

$Db = m/V_0$.

The increase in bulk density of a powder is related to its cohesiveness.

Tapped density (D_t)

Required grams of powder (m) was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant weight in a tap density tester and tapped volume (V_i) was read. The tapped density was calculated using the following formula,

$Dt = m/V_i$

Carr's Index (CI)

The simplest way for measurement of free flow of powder is compressibility. Compressibility indices are a measure of the tendency for arch formation and the ease with which the arches will fall and as such, it is a useful measure of flow. Carr's index is calculated as follows

$C.I = [(D_t - D_b)/D_t] \times 100$

Hausner's Ratio (HR)

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula

$HR = D_t/D_b$

Angle of repose (θ)

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Open ended cylinder method was used. When powder was poured into an open ended cylinder after placing onto a horizontal surface, it forms a cone. The angle is a measure of the cohesiveness of the powder, as it represents the point at which the inter particle attraction exceeds the gravitational pull on a particle. A free - flowing powder will form a cone with shallow sides and hence a low angle

Table 5: Pre-compression parameters results.

Parameter	F1	F2	F3	F4	F5	F6
Bulk density (g/ml)	0.326	0.327	0.337	0.310	0.321	0.334
Bulkiness (ml/g)	3.067	3.058	2.967	3.226	3.115	2.994
Tapped density (g/ml)	0.375	0.355	0.59	0.367	0.36	0.388
Angle of repose (º)	35.41	31.15	33.07	37.30	40.10	37.30
Carr's Index (%)	13.15	8.11	8.57	15.3	10.8	13.89
Hausner's ratio	1.15	1.08	1.09	1.18	1.12	1.16

Table 6: Post-compression parameters results.

Parameter	F1	F2	F3	F4	F5	F6
Thickness (mm)	4	4	4	4	4	4
Diameter (mm)	8	8	8	8	8	8
Hardness (kg/cm^2)	6.6 ± 0.8	5.73 ± 0.611	7.06 ± 1.026	6.26 ± 0.902	6.13 ± 0.503	5.93 ± 0.611
Uniformity of weight (mg)	244.4 ± 7.265	242.5 ± 8.864	238.9 ± 13.64	241.1 ± 6.009	240 ± 8.66	245.6 ± 7.265
Friability (%)	0.0771	0.1115	0.0283	0.0899	0.4458	0.0625
Drug content/ Assay (%)	88	97.4	94.6	91	94.4	99

Table 7: Comparison of drug release profiles of all formulations.

Time (hr)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	91.8	89.1	36.9	34.2	34.2	35.1
2	92.7	90	54.9	46.8	41.2	46.8
3			79.2	63.9	57.4	62.1
4			89.1	80.1	70	72.9
5			99.9	88.2	79	82.8
6				92.7	91.6	89.1
7				98.1	93.4	97.2
8				98.1	98.8	99.9

of repose, while a cohesive powder will form a cone with steeper sides.

$\theta = \tan^{-1} (h / r)$

Where, h: height of the pile.

r: radius of the base of the pile.

Application

During tabletting, improper flow of granules from the hopper leads to under – fill or over filling of die cavity. As a result, tablets will have weight variation and content uniformity.

Post-Compression Parameters

Appearance

The tablets were examined externally under a biconvex lens for the surface, colour, polish etc.

Dimensions

The dimensions of the tablets are thickness, diameter. These were measured using vernier callipers. The dimensions of three tablets were measured and average, standard deviation were calculated.

Hardness

The hardness (diameter crushing strength) is the force required to break a tablet across the diameter. It is an indication of strength of the tablet. The hardness of tablets were measured using pfizer hardness tester**.** Three tablets were selected from each formulation and the hardness was measured by placing the tablet across the diameter in between the spindle and the anvil. The reading of the pointer is adjusted. The pressure was increased slowly to break the tablet. The average and standard deviation of hardness were calculated.

Weight Variation

This is an important in-process quality control test to be checked frequently. Any variation in the weight of the tablet leads to either under medication or overdose. Ten tablets of each formulation were weighed individually and the average weight was calculated from total weight of all the ten tablets. The individual weights were compared with the average weight. The percentage deviation in the weight variation should be within the permissible limits.

% Deviation = [(Individual weight-Average weight)/Average weight]×100

Friability

Friability test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation and shipment. To measure the strength of the tablet, friability test is carried out. It was carried out using roche friabilator. It consists of a plastic chamber which rotates at 25rpm. Tablets were initially weighed and placed in the chamber of friabilator. In the friabilator, tablets were exposed to rolling, resulting from the free fall of tablets in the chamber to a distance of 6 inches. After 100 revolutions (i.e., 4min) the tablets were taken out from the friabilator and tablets were reweighed. Percentage friability was calculated using the formula given below:

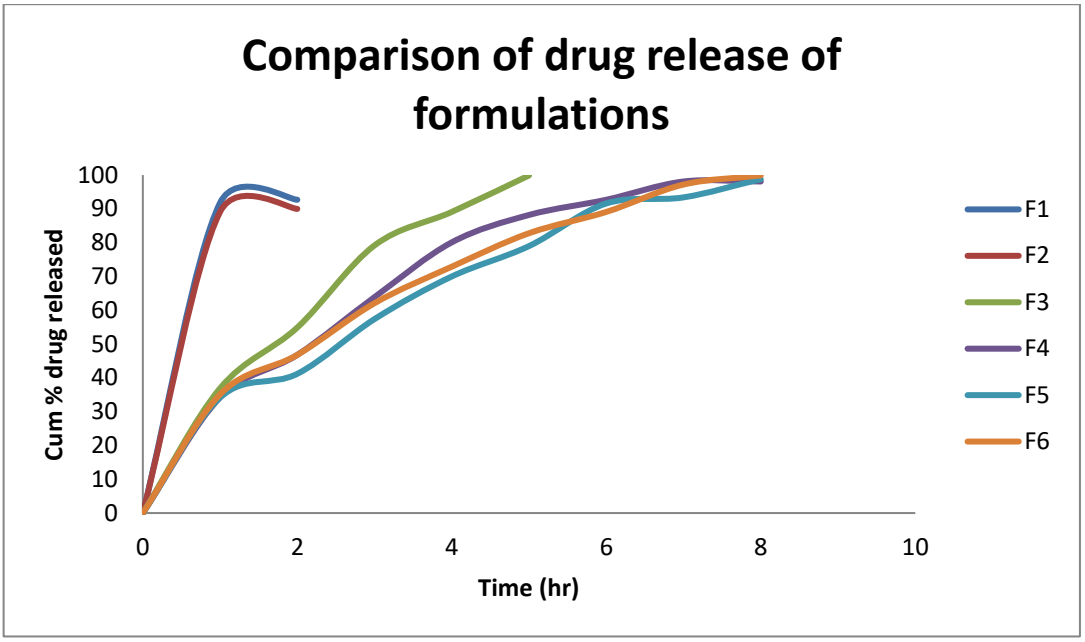

Figure 11: Comparison of drug release profiles of all formulations.

% Friability = $[(w_1-w_2)/w_1] \times 100$
where, w_1 is weight of the tablets before test
w_2 is weight of the tablets after test

In vitro Drug Release Studies

Dissolution is the process in which a solid substance solubilizes in a given solvent i.e., mass transfer from the solid surface to the liquid phase. Dissolution test is done for measuring time required for a given percentage of drugs in a tablet or a capsule to form solution under specified conditions for *in vitro*. Tablets dissolution was carried out in USP Type-II dissolution apparatus (paddle apparatus) by using different buffers *viz*. pH 1.2 buffer, acetate buffer pH 4.5, phosphate buffer pH 7.4 as dissolution medium. 900ml of dissolution fluid was transferred into the dissolution flask and temperature is maintained at 37 ± 0.5^0C. The tablet was placed into the dissolution flask and the rotation speed was adjusted to 50 rpm or as directed in the individual monograph. The test was carried out in three different buffers initially in pH 1.2 buffer for 2 hrs, next 2 hrs in acetate buffer pH 4.5 and finally 4 hrs in phosphate buffer pH 7.4 in order to simulate the environment in the gastrointestinal tract. Samples were withdrawn for every hour time interval and the amount of the drug released at that particular time was calculated from the absorbance values that were determined spectrophotometrically at 271 nm using UV-spectrophotometer.

Dissolution rate test conditions:
Apparatus - USP Type-II, Paddle Method
Dissolution Medium - pH 1.2 buffer for first 2 hours, pH 4.5 acetate buffer for next 2 hours and pH 7.4 phosphate buffer for next 4hrs
RPM - 50
Sampling intervals (hrs) - 1,2,3,4,5,6,7,8
Temperature - 37°c ± 0.5°C

Drug content/Assay

One tablet was taken in a mortar and powdered, then it is taken into 100 ml volumetric flask and dissolved in small amount of phosphate buffer pH 7.4, the volume was made up to the mark with pH 7.4 phosphate buffer and sonicated for 30 min. The obtained solution was filtered and the filtered solution was suitably diluted and assayed for Tramadol hydrochloride content by measuring absorbance at 271nm using UV- Spectrophotometer.

$$\%\ Drug\ content = \frac{test\ absorbance \times dilution\ factor \times volume\ of\ buffer}{slope \times 1000}$$

RESULTS AND DISCUSSION

Standard calibration curve of Tramadol hydrochloride in pH 1.2 buffer, acetate buffer pH 4.5 and phosphate buffer pH 7.4 were drawn by plotting absorbance v/s concentration. The λ_{max} of Tramadol hydrochloride in all the three buffers was determined to be 271nm as shown in Fig. 4.1.1, Fig. 4.1.3 and Fig. 4.1.5. The absorbance values were tabulated in Table 4.1.1, Table 4.1.2 and Table 4.1.3 for pH 1.2 buffer, acetate buffer pH 4.5 and phosphate buffer pH 7.4 respectively. Standard calibration curve of Tramadol hydrochloride in the Beer's range between 20-100 µg/ml were shown in Fig.4.1.2, Fig.4.1.4 and Fig.4.1.6 for pH 1.2 buffer, acetate buffer pH 4.5 and phosphate buffer pH 7.4 respectively.

Dose Calculation

Total dose = Initial dose + Maintenance dose
Total dose = Initial dose + $[1 + (0.693t/ t_{1/2})]$
Where, t is the time required for the release
$t_{1/2}$ is the half-life of the drug
$D_t = 50\{1+ [(0.693\times8)/6.3]\}$
$D_t = 50\{1+ (5.544/6.3)\}$
$D_t = 50\{1+0.88\}$
$D_t= 50\ (1.88)$
$D_t= 94 \sim 100$mg

Drug – Excipient Compatibility Study

Fourier Transmission Infrared Spectroscopy:
Drug – excipient compatibility study was carried out using FTIR. The spectra of the pure drug, the physical mixture containing polymers were taken, the FTIR spectra were as below. All the peaks that are to be present in the drug were present in the spectrum representing all functional groups like cyclohexane, aromatic ring, 3^0 amine, alcoholic group, ether group etc. All the peaks were there in IR spectra of physical mixtures even indicating that there were no incompatibilities between the drug and the other excipients.

Differential Scanning Calorimetry

Differential scanning calorimetry was performed to study the drug-polymer interaction. The DSC thermograms of Tramadol hydrochloride and physical mixture of optimized formulation did not show much change. It is therefore, expected the drug and polymer are compatible and free from chemical interactions as shown in the Fig 9 and Fig 10.

Selection of polymer

Based on the literature review and availability of polymers, we have formulated trial formulations using three different polymers namely HPMC 100 MCR, HPC and Ethyl cellulose 7cps and all the three polymers had the ability to show sustained release of drug for 8hrs duration.

Selection of best formulation

Various combinations of these three polymers were taken in varying ratios and the drug release were studied by dissolution studies and it was observed that

F1 and F2 formulations that were prepared by combination of HPC and EC with different concentrations. As the drug is released within 2hrs, these formulations and this combination was not fit for the objective of the work.

Hence, the combination of polymers was changed by taking the combination of 3 polymers (HPC, HPMC and EC) and 2 polymers as HPMC, HPC and HPMC, EC.

In F3, it was observed that though the drug release was within 5hrs, it was not upto the mark as stated in the objectives.

Formulations F4 and F5 were prepared by combination of HPMC and EC and observed that the release was as per the stated objective i.e., for 8hrs and the amount released was almost similar for both the formulations with minimum variation.

The other combination i.e., HPMC and HPC was formulated as F6 and the release was as per objective.

Of all the 6 formulations, F6 containing HPMC and HPC in equal proportions was considered as best one based on various evaluation tests and *in vitro* drug dissolution studies.

Evaluation

Pre-Compression Parameters

The numerical values of pre compression parameters like Hausner's ratio, carr's index and angle of repose were within the official limits and suggested excellent flow properties for all formulations as mentioned in the Table 5.

Post-Compression Parameters

All tablets of all formulations were elegant and are off-white to white in colour with smooth surface.

In vitro Drug Release Studies

The main aim of the present work was to attain prolonged dissolution of the drug (i.e. in about 8 hours). The required dissolution profile of the prepared formulations was obtained as the prepared tablets showed prolonged release for about 8hrs. The drug release varied from a period of 2hrs to 8hrs for various formulations.

CONCLUSION

This work is done in order to formulate sustained release matrix tablets of Tramadol hydrochloride for pain relief and better patient compliance. In the present investigation, an attempt was made to develop matrix tablets of Tramadol hydrochloride to achieve sustained release of the drug for required duration i.e., 8hrs. Drug and excipients studies were conducted using FTIR. Matrix tablets were formulated using HPC, HPMC K100 and EC 7cps as release retardants or matrix forming agents; Aerosil as glidant; Magnesium stearate as lubricating agent and Microcrystalline cellulose as vehicle or diluent. Direct compression method was used for the preparation of tablets. As the drug was found to be more aqueous soluble, hydrophobic matrix forming polymers were used for formulation of sustained release tablets. Tramadol hydrochloride sustained release matrix tablets were evaluated for appearance, dimensions, weight variation, hardness, friability, *in* vitro drug release and % drug content. The comparative release studies revealed that the release rate was dependent on the polymer combination and concentration of the polymers used. No drug-excipients interactions were observed. The characterization studies depicted the purity of drug & all the excipients used in the formulation. The IR spectrum of mixture of Tramadol hydrochloride with all other excipients does not show any changes which indicate its incompatibility with other excipients and DSC thermograms of pure drug and best formulation showed same melting points indicating that there is no change in the properties of drug.

From the results, it can be concluded that the prepared matrix tablets of Tramadol hydrochloride showed sustained release of drug for a period of 8hrs. Thus the prepared Tramadol hydrochloride matrix tablets could be a better alternative for achieving sustained action of drug thus resulting in a better therapy to treat pain, arthritis and to achieve improved patient compliance.

ACKNOWLEDGEMENTS

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REFERENCES

1. Navin Dixit, Sheo Dutt Maurya, Bhanu, Sagar P.S. Sustained Release Drug Delivery System. Indian J. Res. Pharm. Biotechnol. 2013; 1(3): 305-310.
2. Raghavendra Rao N.G*, Gandhi Sagar, Patel Tarun. Formulation and Evaluation of Sustained Release Matrix Tablets of Tramadol Hydrochloride. IJPPS. 2009; 1(1): 60-70.

3. Drug Delivery Systems, edited by Kewal K. Jain. Humana Press. 2008

4. Jens. T. Caratensen. Advanced Pharmaceutical Solids, edited by James Swarbrick. Marcel Decker, Inc. New York, Basel, 2001.