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A comparative study of Okra gum on controlled release kinetics and other formulation characteristics of Tramadol HCl extended release matrix tablets Vs Synthetic hydrophilic polymers.

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Abstract

The main aim of this investigation was to develop a sustained release matrix tablets of Tramadol HCl using hydrophilic polymers such as hydroxyl propyl methyl cellulose (HPMC), in different grades (E15LV, K4M, K100M) and compare the various parameters against the natural polysaccharide Okra gum. The polymer proportions are used in different concentration in order to optimize the correct proportion of polymer to achieve controlled release profile. The matrix tablets were prepared by direct compression technique which is more industrially relevant. A small quantity of Carbopol was also incorporated in the formulation to give bio-adhesiveness & improved compression characteristics. The formulations were studied for pre-compression parameters and post-compression parameters. The *in vitro* drug release study was performed in 0.1N HCl (pH 1.2) for 1.5 hour and phosphate buffer (pH 6.8) were upto 12 hours. The study results revealed that the matrix tablet can be developed with the used polymers without any tablet manufacturing defects in optimized polymer concentration.. The polymers could control the drug release in various levels according to the concentration present in the formulation. The drug release profile was fitted with various pharmacokinetics models. The formulations showed the different degree of fit with different kinetic models. The drug release mechanism involves the combined process of diffusion, swelling and erosion.

Keywords: Tramadol HCl, HPMC E15LV, HPMC K4M, HPMC K100M, Okra gum, Matrix tablets.

Introduction

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. The drug delivery systems, available in the market are mostly of oral drug delivery systems. Oral drug delivery systems have progressed from immediate release to site-specific delivery over a period of time. The kinetics of drug release will be dependent on the specific prolonged action mechanism utilized in manufacturing the controlled release system. The effort to develop a delivery system that release drug slowly must be directed primarily at altering the release rate by affecting the value of K_1 (K_1 = First order rate constant for drug release. [1] The controlled release system is to deliver a constant supply of the active ingredient, usually at a zero-order rate, by continuously releasing, for a certain period of time, an amount of the drug equivalent to the eliminated by the body

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks flexible (synovial) joints. About 1% of the world's population is afflicted by rheumatoid arthritis, women three times more often than men. Onset is most frequent between the ages of 40 and 50, but people of any age can be affected. [2, 3] The pathology of the disease process often leads to the destruction of articular cartilage and ankylosis (fusion) of the joints. Rheumatoid arthritis can also produce diffuse inflammation in the lungs, membrane around the heart (pericardium), the membranes of the lung (pleura), and white of the eye (sclera), and also nodular lesions, most common in subcutaneous tissue. Although the cause of rheumatoid arthritis is unknown, autoimmunity plays a pivotal role in both its chronicity and progression, and RA is considered a systemic autoimmune disease. In addition, individuals with the HLA-DR1 or HLADR4 serotypes have an increased risk for developing the disorder. It can be a disabling and painful condition, which can lead to substantial loss of functioning and mobility if not adequately treated.[4]. Various treatments are available for RA such as Non-pharmacological treatment includes physical therapy, orthoses, occupational therapy and nutritional therapy but these do not stop the progression of joint destruction. Analgesic and anti-inflammatory drugs, including steroids, are used to suppress the symptoms, while disease-modifying anti-rheumatic

drugs (DMARDs) are required to inhibit or halt the underlying immune process and prevent long-term damage.[5]

Tramadol hydrochloride is a centrally acting synthetic analgesic used to treat moderate to moderately-severe pain.[6] The drug has a wide range of applications, including treatment of rheumatoid arthritis, restless legs syndrome and fibromyalgia. Tramadol is a very weak μ-opiod receptor agonist, induces serotonin release, and inhibits the re-uptake of norepinephrine.[7] Tramadol is converted to *O*-desmethylTramadol, a significantly more potent μ-opioid agonist. This further distinguishes Tramadol from opioids in general (including morphine), which do not possess Tramadol's degree of receptor subtype selectivity and which are much stronger opiate-receptor agonists. Similarly, the habituating properties of Tramadol (such as they are) are arguably mainly due to μ-opioid agonism with contributions from serotonergic and noradrenergic effects. Tramadol is used similarly to codeine, to treat moderate to severe pain. Pharmacologically, Tramadol is similar to levorphanol (albeit with much lower μ-agonism), both agents have SNRI activity.[8] Tramadol is also molecularly similar to venlafaxine (Effexor) and has similar SNRI effects, with anti-nociceptive effects. Half life of Tramadol is 5-7 hrs, Bioavailability is 50-60%, Protein binding is 20%, Elimination half-life is 23 min. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. Tramadol hydrochloride ER tablets should be initiated at a dose of 100 mg once daily and titrated up as necessary by 100 mg increments every five days for relief of pain and depending upon tolerability. Tramadol hydrochloride ER tablets should not be administered at a dose exceeding 300 mg per day. The developed ER formulation reduces the frequency of administration, increases effectiveness of therapy and reduces the chances of adverse effect and hypersensitivity of reaction by maintaining the plasma drug concentration at the optimum level with in therapeutic range for the required period of time. So the rationale behind the formulation ER tablets of Tramadol becomes clear as to reduce dose frequency as well as side effects. Since Tramadol is known for its side effects. The study is also designed to compare the release profile of the novel polymer Okra gum against available for controlled release HPMC grades .[9]

Natural polymeric gums or mucilage is economical and availability and low toxicity are the value added in these categories. The plant Abelmoschus esculentus is a tall, erect annual plant commonly known as 'Okra'. It is widely cultivated in most tropical countries. Abelmoschus esculentus (L) Moench commonly known as okra is rich in water extractable polysaccharides that can give high viscosity at very small concentrations. The thickening properties of okra gum polysaccharides are utilized as a fat substitute in chocolate bar cookies, egg white substitute and in frozen dairy products.Starch is a major constituent of most plant-based and some muscle-based processed food.[10] Many researches in drug delivery center on are obtained from plants because of their form of applications. Natural gums have been employed as disintegrants, emulsifying agents suspending agents and binders.[11] They have been also found useful in developing immediate and sustained release preparations.[12] Okra gum, a polysaccharide consisting of D-galactose, L-rhamnose and L-galacturonic acid.[13, 14] Okra gum is applied as a binder. In a study okra gum has been valued as a binder in paracetamol tablet formulations. These formulations containing okra gum as a binder demonstrated a faster onset and higher amount of plastic deformation than those containing gelatin. The crushing strength and disintegration times of the tablets increased when higher okra gum binder concentration was used while their friability decreased.[15] Although gelatin produced tablets with higher crushing strength, okra gum produced tablets with longer disintegration times than those containing gelatin. It was finally concluded from the results that okra gum may be a useful hydrophilic matrixing agent in sustained drug delivery devices. It forms a viscous mucilaginous solution in water. This attribute has been used in the output of a plasma expander Abelmoschus esculentus gum (AEG) has likewise been used as suspending and emulsifying agents Recently, the mucilage obtained from Abelmoschus esculentus was reported to cause a sustained release property in tablet formulations.[16-17]

HPMC E 15 LV is hydorxy propyl methyl cellulose ether low viscosity grade polymer. Cellulose ether products are available in two basic types: methylcellulose and hypromellose. Both types of have the polymeric backbone of cellulose, a natural carbohydrate that contains a basic repeating structure of anhydroglucose units. During the manufacture of HPMC, cellulose fibers are heated with a caustic solution which in turn is treated with methyl chloride, yielding the methyl ether of cellulose. The fibrous reaction product is purified and ground to a fine, uniform powder. Methylcellulose (A) is made using only methyl chloride. For hypromellose products (E, F and K), propylene oxide is used in addition to methyl chloride to obtain hydroxypropyl substitution on the anhydroglucose units. This substituent group, -OCH2CH(OH)CH3-, contains a secondary hydroxyl on the number two carbon and may also be considered to form a proplyene glycol ether of cellulose. These products possess varying ratios of hydroxypropyl and methyl substitution, a factor which influences organic solubility and the thermal gelation temperature of aqueous solutions. Cellulose ethers dissolve in water with no sharp solubility limit. This feature provides exceptional handling flexibility and control of solubilization rate.

The scope of this work is to define the competitive controlled release properties of okra gum against the famous controlled release modern versions of polymers such as HPMC E and K grades. The premium version of the HPMC polymers are known for their superiority in performance and flexibility in the handling in controlled release systems based on matrix and reservoir type of mechanism. In current pharmaceutical industry HPMC is the integral part of the novel drug delivery system.[21] This research is designed to explore the competitive potential of Okra gum in controlled release and extended drug release systems against the already known HPMC different grades. The tablets are prepared

by direct compression since it is industrial relevant. Okra gum being a natural polymer which has many advantages over the synthetic and semi synthetic polymers. The study also focused on rheumatoid arthritis by using the model drug Tramadol HCl because Tramadol is used similarly to codeine to treat moderate to severe pain. The controlled release Tramadol HCl devices offers the concentration of the drug within the therapeutic window for the extended period of time to increase patient convenience,.

The main objective of the present study is to develop a extended release tablets of Tramadol HCl by using Okra gum and different hydrophilic polymers. The extended release tablets were prepared by direct compression method which is industrially relevant. The polymers such as HPMC K4M, HPMC E15LV, HPMC K100M, Carbopol 940, Okra gum, was used in the formulation design. The exipients such as Microcrystalline cellulose, Magnesium stearate, and Talc were used as an excipients. The evaluation of blend characteristics of prepared granules and evaluation of Post – compression parameters of Tramadol extended release tablets was also carried out. The *in vitro* release characteristics of all formulations were done by using USP dissolution apparatus type II (paddle). The Mechanism of drug release was analysed by using various kinetic models and the results were discussed ornately.

The main objective of the present study is to develop a extended release tablets of Tramadol by using Okra gum and different hydrophilic polymers.containing extended release polymers that will release the drug for a prolong period thus maintaining plasma level for desired time period was designed as the opitimized formulation. The extended release tablets were prepared by direct compression method which is industrially relevant. The polymers such as using HPMC K4M, HPMC E15LV, HPMC K100M, Carbopol 940, Okra gum, was used the final design. The exipients such as Micro crystalline cellulose, Magnesium stearate, and Talc. The evaluation of blend characteristics of prepared granules and evaluation of Post –compression parameters of Tramadol extended release tablets also carried out. The *in-vitro* release characteristics of all formulations were done by using USP dissolution apparatus type II (paddle). The Mechanism of drug release was analysed by using various kinetic models and released results were presented in this article.

Materials and Methods

Material

The materials used in the experiment are of analytical grade. The model drug Tramadol Aurobindo pvt. Ltd, Hyderabad, India. HPMC K4M, HPMC E15 LV and Carbopol 940 were procured from Loba chemie pvt. Ltd Mumbai, India. HPMC K100M was from Otto chemicals, Mumbai, India. Magnesium stearate was obtained from SD fine-chem. Ltd. Mumbai. Talc and MCC from Merck specialities pvt Ltd, Mumbai, India. Okra gum was prepared in the Institute.

Preformulation study

The Preformulation study such as identification test, Angle of repose, Bulk density, Tapped density, Compressibility index (Carr's index), Hausner's Ratio were carried out as per the standard procedure (Ofoefule et al., 2001). Drug - Excipient Compatibility Studies were also performed by using FTIR and DSC analaysis.

FTIR study

The drug polymer interactions were analyzed by FTIR spectrophotometer, Perken-Elmer (spectrum-100 Japan). Two percent w/w of the sample, with respect to potassium bromide (KBr, SD Fine Chem. Ltd, Mumbai India) disc, was mixed with dry KBr. The mixture was ground into a fine powder using an agate mortar and then compressed into a KBr disc in a hydraulic press at a pressure of 10000 Psi. Each KBr disc was scanned 16 times at 2mm/size at a resolution of $4cm^{-1}$ using Carson apodization. The characteristic peaks were recorded.[18]

DSC Differential Scanning Calorimetry study

DSC thermogram were obtained using an automatic thermal analyzer system. Temperature calibration was performed using indium as the criterion. Samples were crimped in a standard aluminum pan and heated from 50 - 300 °C at a heating rate of 10 °C/min under constant purging of nitrogen at 30ml/min. An empty pan sealed in the same manner as the sample was used as a reference.[19]

Preparation of Okra gum

Extraction of mucilage: The fresh Abelmoschus esculentus fruits were collected and washed with water. Incisions were made on the fruits and left over night.The fruits were crushed and soaked in water for 5–6 hours, boiled for 30 minutes and kept aside for 1 hour to allow complete release of the mucilage into the water. The mucilage was extracted by using a multi layer muslin cloth bag to remove the marc from the solution. Acetone (three times the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 40 C, collected, ground, passed through a # 80 sieve and stored in desiccator at 30 C and 45% relative humidity till use.[20]

Fabrication of extended release tablets of Tramadol HCl

Extended release tablets containing 100mg of Tramadol HCl were prepared by direct compression method by employing HPMC K4M, HPMC E15LV, K100M, Carbopol 940 & okra gum as rate controlling polymers, MCC was used as a diluents. Talc and Magnesium stearate was used as a glidant and lubricant. All the materials were weighed according to the formula given in the Table 1. Accurately weighed quantity of drug was then mixed thoroughly with required quantity of polymers HPMC K4M, HPMC E15LV, HPMC K100M and Okra gum as a separate batches. Carbopol940 was added in each batches in increasing proportion. The diluents MCC was added in the formulation and then lubricated with

required quantity of Talc and Magnesium stearate. The powder was then compressed in Rotary tablet punching machine by using 12mm and 8mm round shaped punches to form a tablets.[22]

Post-Compression Evaluation

The post compression parameters such as thickness, Hardness, friability, Drug content uniformity, weight variation were analysed by standard procedures. [21]

In-vitro release studies

Procedure for dissolution.

The release of Tramadol ER tablet was carried out in USP Type II dissolution apparatus 900 ml of 1.2 pH buffer as dissolution medium for 1.5 hr at 100 rpm and 37 ± 0.5 ^{o}C was maintained throughout the experiment. In buffer stage HCl is replaced with 6.8 pH buffer solution. An aliquot (5 ml) was withdrawn at specific time intervals and drug content was determined by UV-visible spectrophotometer at 270.5 nm. An equal volume of fresh dissolution medium was replaced to maintain the sink condition. Samples were withdrawn at regular time intervals. Drug content was determined by UV spectrophotometer at 270.5 NM. Cumulative percentage of drug release was calculated by using an equation obtained from a standard curve.

Drug release kinetics and mechanism of drug release

The dissolution profile of all batches of the formuations was fitted with Zero order. First order, Higuchi model and Korsmeyer - Peppas model to ascertain the kinetic modeling of drug release. Correlation coefficient (R^2) values were calculated for linear curves obtained by the regression analysis of the drug release model.

Zero order kinetics, it describes the system in which the drug release rate is independent of its concentration.$Qt=Q_0+K_0 t$ .Where the Qt= amount of the drug dissolved in time t and the Q_0 = initial amount of drug in the solution, which is often zero and K_0 is the zero order release constant. If the zero order drug release kinetic is obeyed , then a plot of Qt versus t will give a straight line with a slope of K_0 and an intercept at zero.

In first order kinetics, it describes the drug release from the system in which the release rate is concentration dependent. Log Qt =log Q_0 + Kt/2.303.Where Qt is the amount of drug released in time t. Q_0 is the initial amount of drug in the solution and K is the first order release constant. If the first order drug release kinetic is obeyed, then line with a slope of Kt/2.303 and an intercept at t=0 of log Q_0.

Higuchi's Model

Drug release from the matrix devices by diffusion has been described by Higuchi's classical diffusion equation: $Q = [D\varepsilon/\tau (2A-CS) CSt]$ ½. 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, CS = The solubility of drug in the matrix, ε = Porosity of the matrix, τ = Tortuosity, t = Time at which amount of drug released. When the data is plotted as Cumulative % drug released Vs square root of time yields a straight line, indicating that drug release follows diffusion mechanisms. The slope is equal to 'K'.[23]

Korsmeyer – Peppas model

The invitro release data were fitted to the well known exponential. Which is often used to describe the drug release behaviour from polymeric systems. Mt/M = Ktn , Where, Mt/M = The fraction of drug released at time't', K = Constant incorporating structural and geometrical characteristics of the drug/polymer system, N = Diffusion exponent related to the mechanism of drug release. When the data plotted as log % drug released Vs log time yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y-intercept.[24]

Hixson – Crowell model

In Hixson-Crowell cube root law the equation can be written as $Q_O^{1/3} - Qt^{1/3} = K_{HC} t$. Where Q_t is the amount of drug release in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for the Hixson-Crowell rate equation.

Results and Discussions

In this study the different grades of Hydroxy Propyl Methyl Cellulose (HPMC K4M, HPMC E15LV, HPMC K100M) were used for the development of Tramadol HCl extended release tablets (F1-F9). The natural polysaccharide such as Okra gum also used in the development of Tramadol HCl ER and matrix tablets. (F10-F15). Every formulation incorporated with the small increments (80, 100 and 120mg) of Carbopol 940 to improve compression characteristics of matrix formulation. It also offers the bioadhesiveness for the disintegrated granules. The influence of Carbopol 940 was also studied in the drug release profile. The excipients such as Microcrystalline cellulose was used as a diluent to increase the bulk of the granule. Talc and magnesium stearate were used as lubricants in the formulation design**.** Drug polymer interactions and compatibility was studied by comparing FTIR spectra of the pure drug with the mixture of drug with other ingredients. As shown in Figures 1 & 2. Tramadol HCl exhibited the peak at 1176.62cm^{-1}, which indicated the presence of nitrogen group. The peaks at 3635.94cm^{-1} also observed due to the presence of inter-molecular hydrogen bonding. The peaks at 1136.11cm^{-1} was due to the presence of oxygen. The peaks present in the drug, with excipients physical mixture also shows and the peaks of Tramadol HCl at 1174.69cm^{-1}, 3699.59cm^{-1}, 1134.1cm^{-1} as intact. The frequencies of functional groups of pure drug remained unaffected in physical mixture containing different polymers and other ingredients. Hence there was no interaction between the drug and excipients used in the study.

Table 1: Formula of Extended Release tablets of Tramadol HCl

Ingredients (mg/tablet)	Formulations														
	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9	FT10	FT11	FT12	FT13	FT14	FT15
Tramadol HCl	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
HPMC K4M	100	125	150	-	-	-	-	-	-	-	-	-	-	-	-
HPMC E15LV	-	-	-	125	150	175	-	-	-	-	-	-	-	-	-
HPMC K100M	-	-	-	-	-	-	150	175	200	-	-	-	-	-	-
Okra gum	-	-	-	-	-	-	-	-	-	25	50	75	100	125	150
Carbopol 940	80	100	120	80	100	120	80	100	120	80	80	80	80	80	80
Magnesium stearate	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.2	1.2	1.2	1.2	1.2	1.2
MCC	114.4	69.4	24.4	101.2	45.8	20.6	14.4	20.1	0.4	89	66	35	16	0.4	0.4
Talc	4	4	4	4	4	4	4	4	4	3	3	3	3	3	3
Total weight	400	400	400	411	401.8	421.2	400	400	420	300	300	300	305	300	320

Figure 1: FT-IR Graph of Tramadol HCl (Pure Drug)

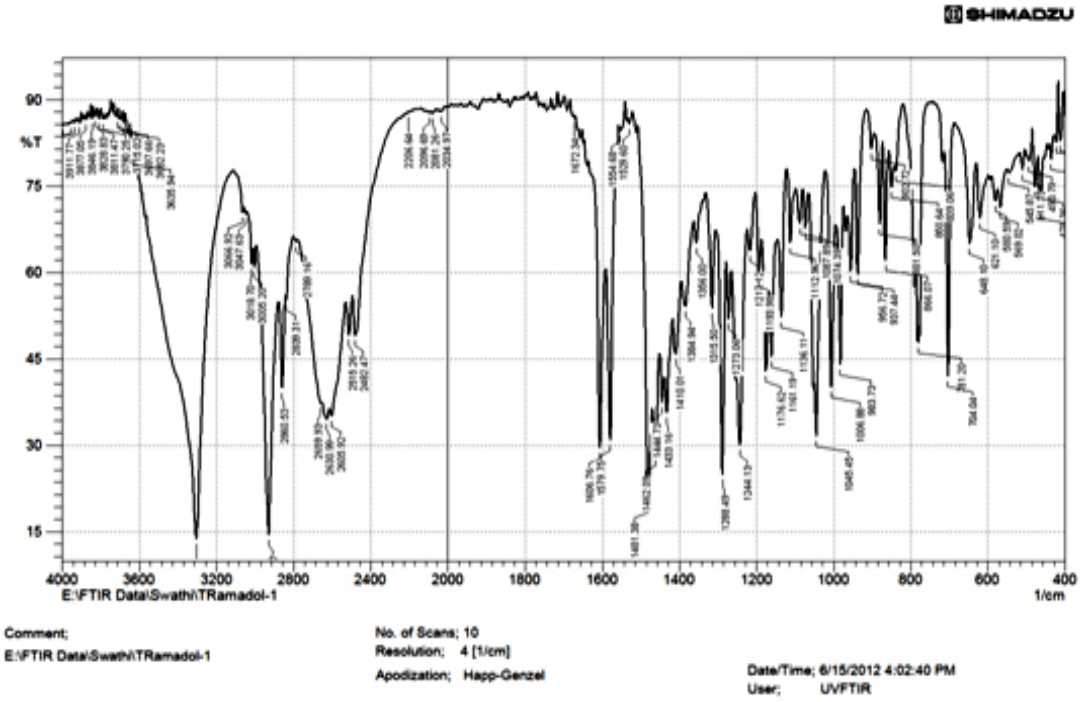
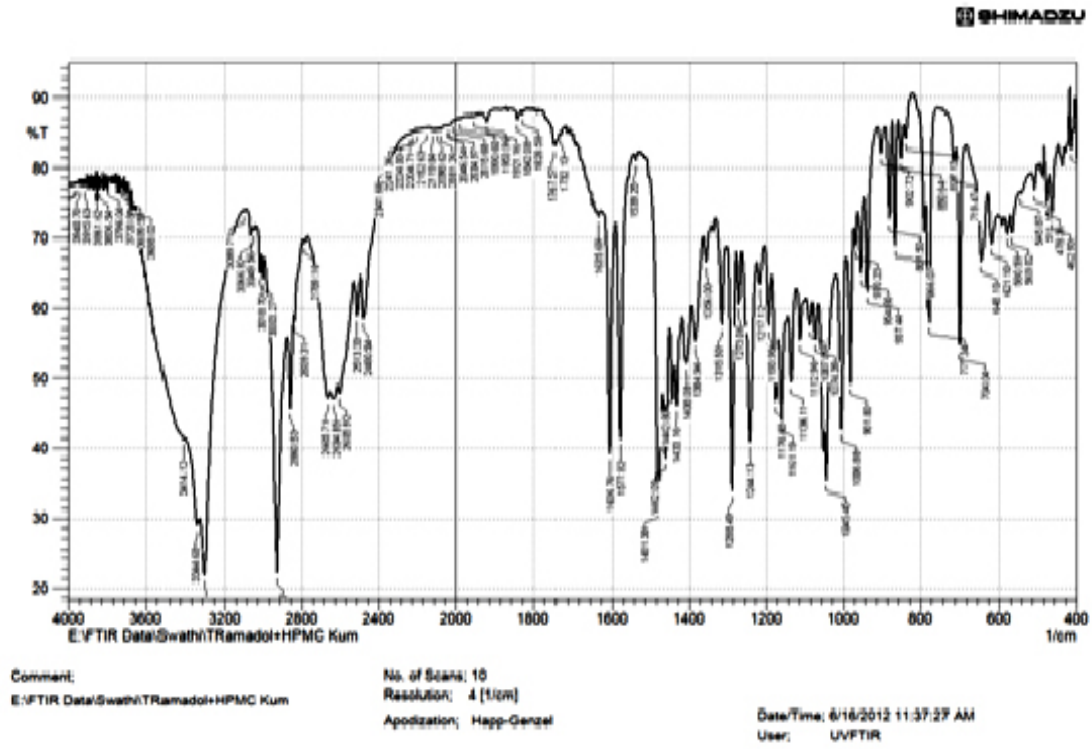


Figure 2: FT-IR Graph of Tramadol HCl + HPMC K4M + Other Excipie



This was confirmed by analyzing the drug and used excipients in Differential Scanning Calorimetry (DSC) thermograms. The DSC Thermograms of the pure drug Tramadol HCl and the mixture of drug and other excipients were shown in Figures 3 & 4. A sharp melting point transition of Tramadol HCl pure drug was observed at 183°C as endothermic peak. The onset of transition was started at 181°C. The thermogram of Tramadol HCl and Carbopol showed the endothermic peak at 181.9°C. The thermogram of Tramadol HCl and HPMC K4M showed the endothermic peak at 182.7°C. The thermogram of Tramadol HCl and Okra gum showed the endothermic peak at 184.9°C The endothermic peak of Tramadol HCl and HPMC E15LV shows the peak at 182°C. The DSC peak value as compared to pure drug and the mixture of samples did not affect the drug nature and no major physico chemical changes happened to Tramadol HCl. Before the direct compression of the tablets the powder was evaluated for angle of repose, tapped density, bulk density, compressibility index and hausner's ratio. The formulations F1-F3 prepared with HPMC K4M as a prime polymer which showed the angle of repose between 21-22 with SD of ±0.04-0.06 the compressibility index of these formulations was ranged between 29%, 30% and 28% for F1, F2 and F3 respectively. The Hausner's ratio was between 1.3-1.5. The formulations[F3-F6] prepared with HPMC E15LV showed the angle of repose ranged between 17-23 with the SD of ±0.1-0.5. The Carr's Index of these formulations were 26, 28 and 33 SD of ±0.24-0.67 for F4, F5, F6 respectively. The Hausner's ratio of these formulations ranges between 1.3-1.5. The formulations prepared with HPMC K100M[F7-F9], demonstrated the angle of repose varied between 26-29 with the SD of ±0.3-0.9. The Carr's Index of these formulations was 26, 26, 25 for F7, F8, F9 respectively. The Hausner's ratio of these formulations ranges between 1.2-1.4. The formulations (F10-F15) prepared with Okra gum, showed the angle of repose between 24-30 with the SD of ±0.1-0.5. The Carrs's Index of these formulations was 24, 28, 24, 26, 32 SD of ±0.32-2.57. The Hausner's ratio of these formulations ranges between 1.3-1.5. As shown in Table 2.

Figure 3: DSC Thermogram of Tramadol HCl pure drug

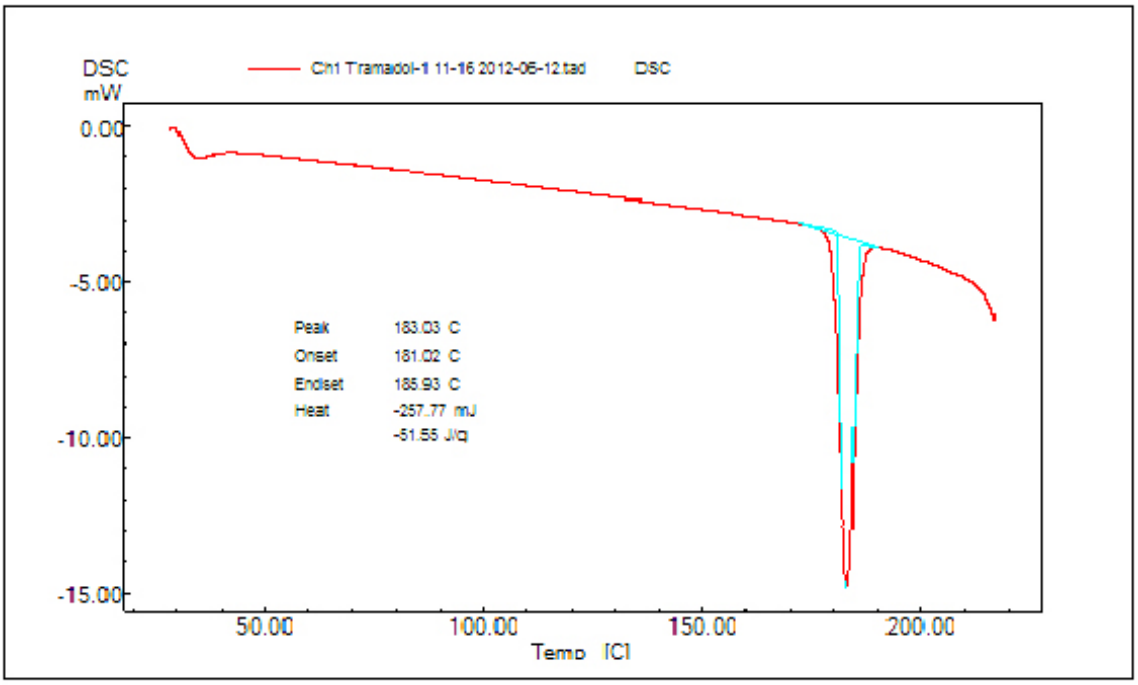


Figure 4: DSC Overlay spectrum of Tramadol HCl, HPMC K4M, HPMC E15LV, Carbopol 940

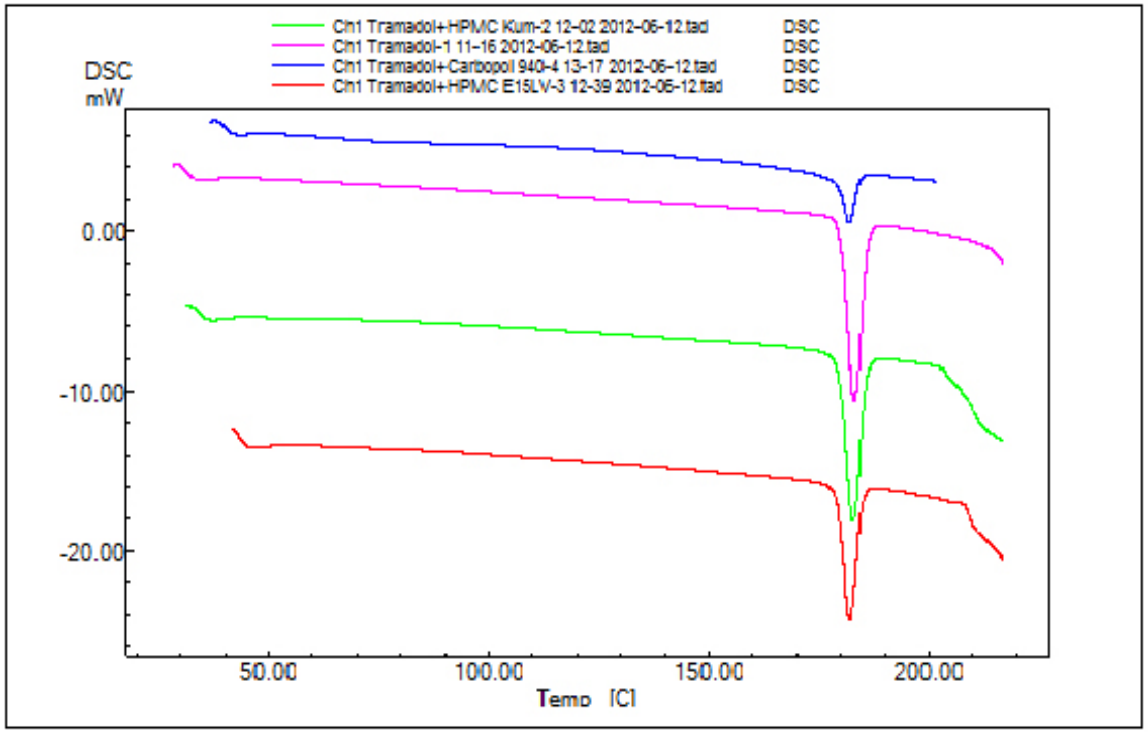


Table 2: Pre compression parameters of the granules

Batches	Angle of repose ( ) ± SD	Loose bulk volume	Tapped bulk volume	Loose Bulk Density (g/cm3) ± SD	Tapped bulk Density (g/cm3) ± SD	Compressibility index (%)	Carr's index (%) ± SD	Hausner ratio
F1	21.8±0.06	24	17	0.41±0.001	0.58±0.003	29.16	29.3±0.32	1.41
F2	21.8±0.05	23	16	0.4±0.002	0.55±0.001	30.4	27.6±0.64	1.37
F3	22.8±0.04	25	18	0.46±0.001	0.62±0.020	28	30.4±2.80	1.55
F4	23.35±0.1	26	19	0.45±0.001	0.52±0.002	26.9	27.14±0.24	1.44
F5	17.3±0.2	25	18	0.44±0.002	0.55±0.004	28	33.18±0.26	1.37
F6	22.78±0.5	24	16	0.46±0.001	0.62±0.006	33	30.012±0.67	1.51
F7	27.69±0.9	26	19	0.44±0.003	0.52±0.01	26.9	23.16±2.00	1.44
F8	29.11±0.9	23	17	0.46±0.003	0.61±0.01	26.2	23.18±0.41	1.20
F9	26.19±0.3	24	18	0.45±0.002	0.53±0.008	25.5	26.21±0.78	1.44
F10	29.03±0.1	26	17	0.45±0.002	0.52±0.008	26.7	30.18±0.73	1.39
F11	24.03±0.1	22	19	0.45±0.002	0.57±0.002	24.3	23.4±0.73	1.35
F12	30.59±0.4	23	18	0.44±0.003	0.54±0.002	32	29.12±2.57	1.32
F13	29.59±0.4	21	16	0.44±0.003	0.60±0.015	28.2	28.16±2.57	1.43
F14	28.66±0.5	25	19	0.43±0.003	0.63±0.015	30.6	33.16±0.32	1.35
F15	27.66±0.5	24	15	0.44±0.003	0.57±0.003	24.4	34.03±0.32	1.53

Evaluation of post- compression Parameters

After the optimization of the pre-compression parameters the HPMC and Okra gum based tablets were compressed in 8 mm round shaped punches at 16 station Cadmach rotary tablet compression machine. The compressed tablets were found to be elegant, smooth in appearance. The tablets were not observed with any formulation defects such as picking, sticking, capping, lamination and cracking. The compressed tablets were evaluated for their weight variation, friability, content uniformity, thickness and diameter. All the parameters were found to be within the limits. The hardness of the formulations F1-F3 was about 5.5-5.8kg/cm^2 with SD of ± 2.7-3.5.The formulations F4, F5, F6 showed the hardness of 5.8-6.18kg/cm^2 with SD of ±1.5-3.00. The hardness of the formulations F7-F9 was 5.7-5.41 kg/cm^2 with SD of ±1-3.60. The formulations F10-F15 showed the hardness of 6.08-6.18kg/cm^2 with SD of ±1.5-2.2. The friability of all the formulations was less than 1 indicated the good integrity of the tablets during handling and packaging. The drug content of the formulation was within the pharmacoepial limits which was confirmed by the appropriate assay procedure [#]. The Thickness of the tablets 2.3-2.5 with SD of ±0.2-0.23. for the formulation F1-F9. The formulations F10-F15 showed the thickness around 4.0-4.5 with SD of ±0.04-0.06 fixing the thickness constant. The content uniformity of the tablets was made within the limits and weight variation was also controlled. As shown in Table 3.

Table 3: Post compression parameters of Tramadol HCl ER and matrix tablets

Batches	Uniformity of weight (n=20±SD) (mg)	Hardness (n=10± SD) (kg/cm^2)	Friability (%)	Thickness (n=20± SD) (mm)	Diameter (mm)	Drug content (%)
F1	398±3.0	5.52±0.32	0.54±0.12	2.15±0.12	12.56	99.29±0.04
F2	396±3.0	5.8±0.41	0.64±0.09	2.51±0.09	12.56	99.46±0.11
F3	395±3.5	5.5±0.47	0.59±0.13	2.54±0.21	12.56	99.66±0.05
F4	398±1.5	5.78±0.29	0.56±0.20	2.38±0.23	12.56	99.23±0.07
F5	396±2.6	5.3±0.18	0.79±0.03	2.56±0.04	12.56	99.49±0.13
F6	394±3.0	6.18±0.07	0.54±0.09	2.52±0.12	12.56	99.72±0.09
F7	397±3.6	5.18±0.07	0.58±0.12	2.55±0.08	12.56	99.29±0.04
F8	396±2.5	5.42±0.32	0.61±0.09	2.54±0.2	12.56	99.46±0.11
F9	399±1.0	5.7±0.41	0.54±0.13	2.36±0.2	12.56	99.66±0.05
F10	298±1.5	6.18±0.07	0.53±0.20	4.11±0.06	8.64	99.23±0.07
F11	298±1.5	6.5±0.47	0.52±0.20	4.30±0.04	8..65	99.23±0.07
F12	297±1.2	6.3±0.18	0.56±0.20	4.21±0.06	8.64	99.49±0.13
F13	297±2.2	6.8±0.29	0.70±0.03	4.52±0.06	8.64	99.49±0.13
F14	299±2.5	6.08±0.07	0.79±0.03	4.01±0.04	8.65	99.72±0.09
F15	294±2.5	6.3±0.18	0.51±0.09	4.56±0.04	8.65	99.72±0.09

In-Vitro drug release study

The *In-vitro* drug release studies were carried out in simulated GIT and p^H conditions (1.2 and 6.8). The formulations were subjected to dissolution studies in 0.1N HCl (1.2 p^H) for 1.5h followed by 6.8 phosphate buffer until the maximum amount of drug was released. The formulations F1, F2, and F3 were prepared with HPMC K4M and Carbopol 940. The formulation F1(1:1) releases 85% of the drug which is extended upto 14h of dissolution profile which contains 20% of carbopol as a secondary polymer to offer muco-adhesiveness and to improve the physico-chemical characteristics of the tablet. The Formulation F2(1:1.25) releases the same amount(85%) of the drug upto 14h of dissolution study. The Formulation F2 showed no significant difference in the dissolution characteristics with F1which is containing 25% of Carbopol. The Formulation F3 contains the aximum amount of release retarding polymer HPMC K4M and Carbopol(30%) shown the slightly improved and extended release profile in the dissolution (80%) upto 14h. Among all HPMC K4M based formulations F3 shown controlled release profile compare to other formulations. The formulations F4, F5 and F6 were prepared with HPMC E15LV and Carbopol 940. Dissolution studies were conducted until the maximum amount of drug release. The formulations F4 and F5 shown 76% and 88% of the drug release respectively, upto 14h of dissolution study. The formulation F6 released the drug bit higher than F4 indicated that the higher amount of HPMC in the preparation controlled the drug release. These formulations also contain 20, 25 and 30% of carbopol in the formulae which also influenced the controled the release to some extent. The formulations F7, F8, F9 controlled the drug release upto 14h. All the three formulations[F7, F8 and F9] released almost same amount of drug that is 85% upto 14h of dissolution profile. These formulations also contains 25, 30, 26% of Carbopol respectively. The formulations F10-F15 prepared with Okra gum with the ratio of 1:0.25, 1:0.5, 1:0.75, 1:1, 1:1.25, 1:1.5. The Okra gum concentration were increased proportionately, where as the Carbopol concentration was kept constant in all the Okra gum based formulation. The formulation design was planned to asses the impact of Okra gum on drug release. So that Carbopol concentration were kept constant. The formulations F10 and F11 released was 84% of drug for 14 h. The formulations F12 and F13 released 82% and 84% of the drug respectively. There was no significant retardation observed between F12 and F13. The formulation F15 showed highest controlled release which is 75% followed by F14 of 81%. Among all the formulations Okra gum also shown the competitive controlled release property when compared

to commercial synthetic polymers. The physico-chemical properties of the Okra gum based tablets was found to be competitive and equivalent to the tablets prepared with HPMC polymers of different grades. The dissolution profile of triplicate studies were very consistent which confirmed the use of Okra gum as a controlled release polymer.

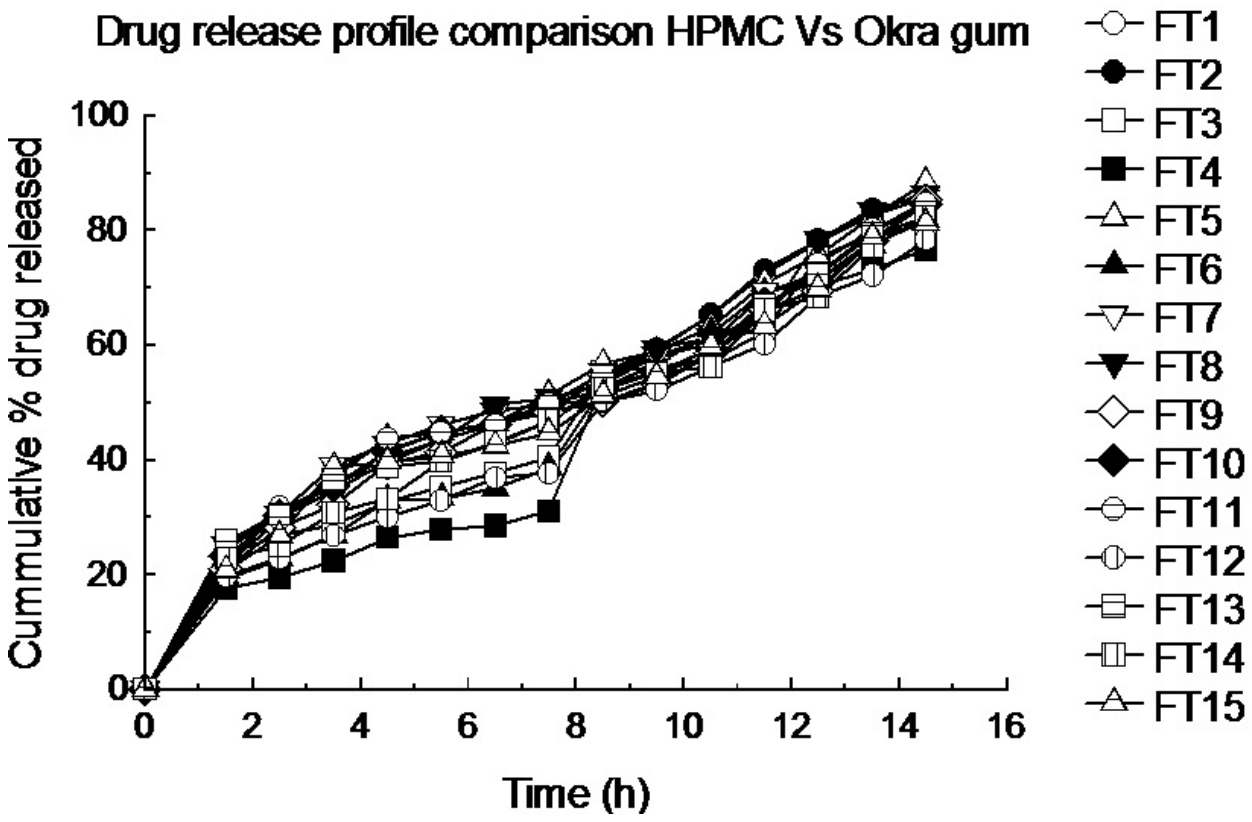
Release Kinetics

The release kinetics of the formulations were studied by fitting the data with different release models. Different formulations were shown the different degree of fit for various release mechanisms such as Zero order, First order, Higuchi's, Korsemeyer Peppa's and Hixson Crowell models. The formulation F1 showed the highest degree of fit with Peppa's equation followed by Higuchi's and Zero order kinetics. The formulation F2 showed the highest degree of fit with Peppa's kinetics followed by Higuchi and Zero order kinetics. In F1 and F2 the release kinetics was also influenced by First order and Hixson Crowell kinetics. The formulation F3 shown the Hixson Crowell kinetics as the predominant release mechanism followed by Zero order and Higuchi's kinetics. The formulations F4, F5 and F6 showed the highest degree of fit with Zero order First order and Higuchi's kinetics. In F5 Korsemeyer Peppa's model was the predominant release mechanism. F6, F7 and F8 shown the highest degree of fit with Kosemeyer Peppa's model followed by Higuchi's and Zero order kinetics. The formulations prepared with F10-F15 showed the Korsemeyer Peppa's as the predominant release mechanism followed by Higuchi's and Zero order kinetics. The mechanism of drug release indicates that more than one release mechanism is involved in every tablet formulation confirms the complexity in drug release mechanism. The involvement of release mechanism in the formulated more than one Extended Release tablets confirmed that the drug release influenced by the swelling, erosion, diffusion and might be by combined mechanism. The Korsmeyer pepllas indicates in the Okra gum based formulation confirmed that the drug release mechanism was influenced by polymer destanglement and geometric changes in the matrix tablets. Which also confirmed that Okra gum is the competitive polymer for matrix design with the advantages of hydrophilic nature, swelling, mucoadhesiveness and controlled release property which confirmed usage of Okra gum as controlled release polymer. As shown in Table 4 and Figure 5.

Table 4: Coefficient of correlation (r^2) values of different Formulations of Tramadol HCl Extended release tablets.

Formulations	Zero order		First order		Higuchi's		Peppa's		Hixson	
	R^2	K_0(mg/hr)	R^2	K_1(hr^{-1})	R^2	KH	R^2	N	R^2	KHC
F1	0.962	5.106	0.923	0.052	0.968	22.17	0.971	0.555	0.941	0.20
F2	0.967	5.201	0.918	0.054	0.962	22.44	0.980	0.040	0.924	0.579
F3	0.965	4.681	0.899	0.046	0.924	21.18	0.911	0.589	0.958	0.263
F4	0.955	5.25	0.932	0.045	0.881	21.18	0.887	0.746	0.922	0.259
F5	0.956	5.049	0.997	1.012	0.967	21.98	0.968	0.543	0.918	0.226
F6	0.977	5.253	0.932	0.048	0.924	22.11	0.980	0.254	0.893	0.496
F7	0.943	4.790	0.997	1.012	0.974	21.06	0.976	0.540	0.847	0.549
F8	0.951	4.979	0.876	0.051	0.958	21.63	0.962	0.535	0.953	0.252
F9	0.958	4.849	0.877	0.046	0.957	20.97	0.973	0.577	0.934	0.437
F10	0.951	4.887	0.926	0.047	0.926	21.36	0.955	0.526	0.874	0.562
F11	0.947	4.729	0.892	0.045	0.967	20.67	0.972	0.529	0.894	0.262
F12	0.971	4.851	0.913	0.044	0.957	20.85	0.962	0.586	0.963	0.589
F13	0.927	4.806	0.870	0.046	0.927	21.68	0.929	0.582	0.963	0.219
F14	0.948	4.704	0.900	0.043	0.955	20.43	0.956	0.562	0.870	0.495
F15	0.977	4.789	0.927	0.041	0.935	20.27	0.944	0.634	0.880	0.495

Figure 5: Drug release profile of Tramadol HCl extended release tablets.



Stability studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. In the present study, Stability study was carried out for the optimized formulations according to ICH guide lines at 2–8 C (controlled sample), Room temperature and 40 c / 75% RH for 3 months. Tablets were evaluated for assay, hardness and friability after three months. The stability study results revealed that there were no significant changes in the crucial parameters such as Assay and hardness, which excludes the stability problems in the developed formulation. Any how long term stability studies are recommended for the formula before the final approval.

Conclusion

The formulated extended release matrix tablets of Tramadol HCl. The extended release tablets showed a sustained release for up to 14h, indicating a promising potential of the Tramadol HCl ER tablet as an alternative to the conventional dosage form. Among the formulations (F1, F2, F3) prepared with HPMC K4M and Carbopol 940 was found to be the best among the formulations (F4, F5, F6) prepared with HPMC E15LV and Carbopol 940, F6 was found to be the best formulation. Among the formulations F7, F8 and F9 prepared with HPMC K100M and Carbopol 940, F9 was found to be the best formulation. Among the Okra gum based formulations F12 and F13 were found to be the best in terms of physio-chemical properties of the tablets and controlling the drug release profile. Okra gum formulations also competitively showed the controlled release as like the cellulose derivative polymers and it is having the property of muco-adhesiveness, biocompatibility, which is the advantage over the HPMC based formulations. Among all the formulations F12 was found to be better in release which follows Zero order, Korsemeyer Peppa's & followed by Hixson Crowell kinetics as a predominant release mechanism. The results of the experimental study confirmed that the polymer concentration significantly influenced the drug release rate. The tablets of optimized formulation F12 (drug polymer ratio of 1:0.75) shown 82.39 % drug release at the end of 14h indicated that it can extend the drug release till the desired time period of 15h. The stability studies indicated that the optimized formulation F12 was stable at short term stability studies, but long term stability studies has to be conducted on tablets to study the changes occurring in various storage conditions. Overall study report suggested that Okra gum can be successfully used as a controlled release polymer by simple industrial relevant direct compression technique.

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