Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Issue 4, 2013

Research Article

FORMULATION AND CHARACTERIZATION OF MATRIX AND TRIPLE LAYER MATRIX TABLETS FOR CONTROLLED DELIVERY OF TRAMADOL HYDROCHLORIDE

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Received: 27 July 2013, Revised and Accepted: 23 Aug 2013

ABSTRACT

Objective: The investigation was concerned with formulation and evaluation of oral controlled release tablets of Tramadol Hydrochloride (THCL) in the form of triple layer matrix tablets using different hydrophilic polymers, Locust Bean Gum (LBG), Gum Ghatti (GG) and Xanthan Gum (XG) as matrix forming agents and layered with hydrophobic Ethyl Cellulose (EC) in order to controlled the drug release beyond 12hrs.

Methods: The core granules and layer granules were prepared by wet granulation technique. The matrix tablets and triple layer matrix tablets were evaluated for Physico-chemical evaluation such a weight variation, thickness, friability, hardness, drug content, *in-vitro* dissolution profiles and FT-IR studies were conducted.

Results and Discussion: The prepared tablets exhibited satisfactory Physico-chemical Properties.

The additions of EC layered on the matrix core were able to control the drug release beyond 12hrs.The MDT and $DE_{8\%}$ valued for F3L1 and F3L3 were found in the range of 12.32hr, 16.66hr and 56.8%, 63.5% respectively. Thus the formulation F3L3 portrays sustained drug release, which was extended for over a period of more than 12hrs. Formulation F3L3 shows $0.04h^{-1}$ the calculated first release rate constant. FT-IR study revealed that, there was no interaction between the drug and excipients used in the study. Analysis of variance (single factor ANOVA) showed a significant differences ($P<0.05$) for the amount of THCL released from the formulations (F3), and formulations (F3L3).

Conclusion: Layering with EC controlled the THCL from the surfaces of matrix core, indicating that triple layer matrix tablets followed linear release profile, extending the release for more than 12hrs. These dosage forms can be developed on large scale using layered tablet press.

Keywords: Tramadol Hydrochloride, Controlled release, Linear drug release, Zero order kinetics.

INTRODUCTION

Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration and flexibility in the design of the dosage form. There are many ways to design modified release dosage forms for oral administration and one of them is multi layered matrix tablet. One to three (multi) layer matrix tablets is a drug delivery device, which comprises a matrix core containing the active solute and one, or more barriers (modulating layers) incorporated during tabletting process [1]. The barrier layers delay the interaction of active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate [2,3]. In the device, the coat layers prevent the water penetration through the protected core for some duration. After this phase during the subsequent dissolution process, the swollen barriers erode and the surface available for drug release slowly increases. In this way the decrease of delivery rate due to the increase in diffusion path length (saturation effect) is counter balanced by the simultaneous increase of the area available for drug release[4,5]. Thus by combining a time-dependent control of the hydration rate of the device, the reduction of tablet surface exposed to the dissolution medium, it is feasible to achieve a linear release profile[6]. The use of naturally occurring biocompatible gums has been the focus of recent research activity in the design of dosage forms for oral controlled release administration, and hydrophilic polymers matrix systems are widely used because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance[7]. Xanthan gum (XG) is soluble in water, anionic hetro polysaccharide and to be sensitive to pH and ionic strengths. Xanthan gum hydrophilic polymer, secreted from Xanthomonas campestris (a Gram-negative, yellow-pigmented bacterium) contains glucose 37%, mannose 43.4%, glucuronic acid 19.5%, acetate 4.5%, and pyruvate 4.4%. It swells in gastric fluid to produce a highly viscous layer around the tablet through which the drug can slowly diffuse[8], and is used for the fabrication of matrices with uniform drug release characteristics[9,10]. Xanthan gum is the bacterial polysaccharide produced industrially on a large scale. It is a natural carbohydrate commercially produced by fermenting glucose with the appropriate micro organisms[11].

LBG is a plant galactomannan, composed of a 1-4- linked β – D mannan backbone with 1-6α-linked D galactose side groups[12]. The galactose content in galactomannan is strongly influenced by the physico-chemical properties. Galactose with longer side chain produces a stronger synergistic interaction with other polymers and greater functionality [13] .

Ghatti gum is a gummy exudation from the stem of Anogeissus latifolia, belonging to the family *Combretaceae*. It is a complex water soluble polysaccharide, occurs in nature as a calcium-magnesium salt. It is composed of L-arabinose, D-galactose, D-mannose, D-xylose, and D-glucuronic acid, with traces of 6-deoxyhexose. The fact that the gum is naturally available, inexpensive and non-toxic has also fostered the interest in developing the gum for pharmaceutical use. Ghatti gum is approved for food use and is in the GRAS (Generally Recognized as Safe) list under the food and Drug Act (US-FDA).

Tramadol hydrochloride (THCL), a synthetic opioid of amino cyclohexanol group, is a centrally acting analgesic. It is an effective centrally acting analgesic with weak opioid agonist properties. Tramadol hydrochloride has plasma elimination half life of 4-6 hrs. The usual dosage regimen is 50-10mg every 4-6 hrs. So, to reduce the frequency of administration and to improve patient compliance, a controlled release dosage formulation of Tramadol HCL is desirable. Tramadol HCL is associated with certain side effects, like abdominal pain, anorexia and it may also induce psychic and physical dependence [14]. Therefore properly designed Controlled Release Dosage Form of this drug will minimize the fluctuation in blood concentration, declining the risk of side effects and will show uniform pharmacological response[15]. The investigation was concerned with formulation and evaluation of oral controlled release tablets of Tramadol HCL in the form of triple layer matrix tablets using different hydrophilic polymers, Locust Bean Gum (LBG), Gum Ghatti (GG) and Xanthan Gum (XG) as matrix forming agents and layered with hydrophobic Ethyl Cellulose (EC) in order to control the THCL release beyond 12hrs.

MATERIALS AND METHODS

Tramadol Hydrochloride was obtained as gift sample from Dr. Reddy Labs, Hyderabad, India, Xanthan gum from Raj enterprises Mumbai,

India. Gum ghatti, from Krystal Colloids, Mumbai, India. Locust Bean gum from Lucid gums Mumbai, India, and Micro Crystalline Cellulose MCC from Reliance Cellulose Product, Hyderabad, India, was used. All other materials were of analytical or reagents grade.

Calculation of Required First order Release Rate Constant [16].

$kr_1 = Ke (exp (-ke \times Ti)$ was the equation used to calculate first order rate constant, (kr_1) of Tramadol HCL from tablets formulation. Where ke is the elimination rate constant ($0.015h^{-1}$) and Ti, crossing time at which the blood level profiles produced by administration, the value of Ti =h-Tp (where 'h' is the duration of therapy, i.e.12hrs in the present study and Tp the time taken for maximum plasma concentration at second hour). This is based on the mean pharmacokinetic parameters of drug in humans and the, first order rate constant was found to be $0.04h^{-1}$. The formulations developed till the required first order rate constant of Tramadol HCL was obtained.

Preparation of Tramadol HCL Matrix Core Granules

Formulations were prepared with three different polymers (locust bean gum, gum ghatti, and xanthan gum). For the formation of the granules, Microcrystalline cellulose (pH 101) was used as diluents, PVP K-30 (5%w/v) solution was used as binding agent. The wet mass was screened through sieve no 16 and the granules were dried at 50°C for 1hr in a tray dryer. The dried granules were passed through sieve no 18 and lubricated with a mixture of talc and magnesium stearate. The composition of formulation used in the study containing 50mg of Tramadol HCl is shown in tables 1.

Preparation of Ethyl Cellulose as Release Retardant Layer Granules

The wet granulation technique was used, ethyl cellulose, lactose and PVP K-30 (5%w/v) were mixed well and the resulting mass was passed through sieve no 16 and dried at 35° C for an hour. The dried granules were passed through sieve no 18, lubricated with talc and magnesium stearate.

Preparation of Matrix and Triple Layered Matrix Tablets of Tramadol HCl

The composition of formulation used in the study containing 100mg of Tramadol HCL in each case is shown in table 1. The granules were compressed using a rotary compression machine. (Riddhi, Ahmedabad, India). The triple layer matrix tablets were prepared by using different tramadol HCL polymers of in 1:1 ratio in the matrix core granule and Ethyl Cellulose as release retarding layer granules. (Tables 1). Initially the volume of die cavity was adjusted equivalent to total weight of triple layer matrix tablets (250mg, 300mg and 350 mg). Then pre-weighed amount of polymer granules of ethyl cellulose equivalent to bottom layer (25mg, 50mg, and 75mg) were taken and placed in the die cavity and uniformly spreaded. The upper punch was lifted up and 250mg of matrix core granules were placed over the bottom layer of polymer granules in the die cavity and slightly compressed. The remaining volume of die cavity was filled with pre weighed amount of polymer granules equivalent to top layers (25mg, 50mg, and 75mg). Finally compressed on a rotary compression machine. The hardness of matrix tablet and triple layer matrix tablets was adjusted to 5-6kg/cm^2.

Physical tests for the Prepared Matrix Tablets

Ten tablets from each formulation were taken for measurement of diameter and crown thickness with vernier calipers and an average of ten determinations was carried out. Hardness of the matrix tablets and triple layer matrix tablets was evaluated by using hardness tester (Pfizer) and mass determination was performed for twenty tablets from each batch and average values were calculated. Friability of the matrix tablets and triple layer matrix tablets was determined by first weighing 10 tablets after de dusting and placing in a friability tester (Roche friabilator, Pharma labs, Ahmedabad, India), which was rotated for 4min at 25rpm. After dedusting, the total remaining weight of the tablets was recorded and the percent friability was calculated. The drug content of the prepared tablets of each batch was determined in triplicate.

***In-vitro* Drug Release Studies**

In vitro dissolution studies for the prepared matrix tablet and triple layer matrix tablets were conducted for a period of 12hrs using a six station (1) USP XXII type II apparatus (Lab India Disso 2000 system, India.) at 37±0.5°C and 50 rpm speed. The dissolution studies were carried out in triplicate for 2h in pH 1.2 medium (900ml) and then the pH of medium was raised to 6.8 by adding 4.6g Sodium hydroxide, 4.005g dibasic sodium phosphate and 3.06g mono basic potassium phosphate at 37±1°C for 10hrs. Samples were collected at specific time intervals and assayed by a UV spectrophotometer (Elico, Model SL-150, Mumbai, India.) at a wavelength of 271nm. The experiments were repeated thrice and the results were taken as average of three test readings with standard deviations. The amount of drug present in the samples was calculated with the help of appropriate calibration curves constructed from reference standards. During the drug release studies, the formulations were observed for physical integrity at different time intervals.

Characterization of Release Data

The description of dissolution profiles has been attempted using different release models. The data were evaluated according to the following equations.

Zero order: $M_t = M_o + K_o t$

First order: $\ln M_t = \ln M_o + K_1 t$

Higuchi model: $M_t = K_H \sqrt{t}$

Korsmeyer –Peppas model: $M_t/M_o = K_k t^n$

Where M_t is the amount of drug dissolved in time t, M_o the initial amount of drug, $K_1$is the first order release constant, K_0 the zero order release constant, K_H the Higuchi rate constant, K_k the release constant and *n* is the diffusional release exponent indicative of the operating release mechanism. The correlation coefficient (r^2) was used as an indicator of the best fitting, for each of the models considered.

The dissolution parameters used for comparing the different formulations was MDT and DE_8%. The following equation was used to calculate the mean dissolution time (MDT) from the mean dissolution data.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M} \quad \text{eq.[1]}$$

Where i is the dissolution sample number, n is the number of dissolution sample time, t mid is the time at the midpoint between i and i-1 and ΔM is the additional amount of drug dissolved between i and i-1[17]. MDT, which is calculated from the amount of drug released to the total cumulative drug. MDT is a measure of the rate of the dissolution process: the higher the MDT, the slower the release rate.

Dissolution efficiency (DE) [18] after 8hr of release test was used to compare the results of dissolution tests of different formulations:

$$DE_8\% = \frac{\int_0^t y\, dt}{y_{100}\, t} \times 100 \quad \text{eq [2]}$$

FT-IR Study

Infrared spectrum was taken (FT-IR, Spectrum RX1, Perkin Elmer Ltd, Switzerland) by scanning the sample in Potassium bromide discs. The samples of pure drug and formulated tablets F3L3 were scanned individually.

Stability Studies

Stability studies were conducted for the optimized formulations F3L3. To assess their stability with respect to their physical appearance, drug content and drug release characteristics after storing at 40°C/75% RH for 3 months. [19]

Statistical Analysis

In-vitro release data of Tramadol HCL from the matrix tablets (F3) and optimized formulations of triple-layer matrix tablets (F3L3) were subjected to the one-way analysis of variance (ANOVA) at different time intervals of drug release upto 12hrs. By applying Newman-Keuls multiple comparison test using Graph pad prism version 4. (Graph pad prism Software, Inc)

RESULTS AND DISCUSSION

In the present investigation, the matrix and Tripled Layered matrix tablets of Tramadol HCL were prepared by wet granulation technique using natural polymers like Locust bean gum Ghatti gum, Xanthan gum in the active matrix core and Ethyl Cellulose (EC) as release retarding layers. The weight of the core matrix tablet was kept 250mg. The ratio of drug: polymer for the core matrix tablet was fixed at 1:1 and layers of different weights of 25mg, 50mg and 75mg was given on both surfaces of the active core to get 300mg, 350mg and 400mg tablets respectively. The formulation was optimized till the desired release rate was achieved. The first order rate constant was found to be $0.040h^{-1}$.

Physicochemical characterization LBG Matrix core and Tripled Layered Matrix Tablets

The prepared tablets were evaluated for physical parameters such as hardness, thickness, friability, weight variation and drug content. The results are shown in Table 2.The mean values for hardness of the layered matrix tablets of Tramadol HCL were in the range of 5.92±0.10 to 6.05±0.03kg/cm^2 All the tablets passed the friability test as the loss the tablet material was less than 1%, indicating that the tablets prepared were of sufficient strength. The layered matrix tablets also satisfied the drug content as they contained 98.15 ±2.25% to 103.2± 2.65% of drug indicating the uniform mixing of the LBG, drug and other formulation excipients.

***In vitro* drug release studies of LBG Matrix core and Tripled Layered Matrix Tablets**

LBG and Tramadol HCL in the ratio of 1:1 as the matrix core, the formulations (F1) showed rapid rate of drug release, when compared to the formulations (F2 and F3). It might be due to degradation of LBG at high pH. The correlation coefficient (r^2) of the LBG matrix tablet (F1) for first order release kinetics was found to be higher (0.9852), when compared to that of zero order kinetics (0.830) indicating that the drug release from the matrix tablets followed first order kinetics. (Table 3). In case of Triple layered matrix tablets, the 'r^2' values for zero order kinetics were found to be higher, when compared to that of first order kinetics. Hence, it may be concluded that, a better controlled drug release can be achieved when a release retardant layer is applied on both sides of the matrix formulation. From the Table 3 it may be observed that, the 'r^2' values for zero order kinetics of 25mg EC layered on both the sides of the matrix core, as in case of 50mg EC layered tablets the 'r^2' values are found to be 0.871 and 0.964 respectively. In case of 75mg EC layered on both the sides of the matrix core, the r value is found to be 0.982. From this data, it can be noted that formulation F1L3 (EC of 75mg on both the surfaces) provides better control over the release than 25mg and 50mg of the EC on both the surfaces of the matrix core. This could be attributed to the high thickness of the layer over the matrix core. From the above study, we may say that 75mg of EC as release retarding agent provided better release to achieve zero-order profile than 25mg and 50mg of the layers on the LBG matrix core, which in turn is even better than simple matrix tablets, shown in Figure 1a. The diffusion coefficient values obtained according to the model developed by Korsemeyer *et al* showed that matrix tablet followed Fickian diffusion and the prepared Triple layered matrix tablets followed non-Fickian diffusion, as the diffusion coefficient 'n' value was found to be less than 0.5 and greater than 0.5 respectively (Table 3). The correlation coefficient values (r^2) for the Higuchi plots ranged from 0.969 to 0.988 for all the tablets i.e., both the matrix and the Triple layered matrix tablets, indicating that the drug release from the tablets occurred by diffusion. Hence, the results indicated that the release of drug Tramadol HCL from the prepared matrix tablet (F1) followed first order kinetics via diffusion controlled mechanism and the prepared triple layered matrix tablets followed zero order kinetics via diffusion controlled mechanism. The MDT and $DE_{8\%}$ of the prepared formulations were calculated shown in Table.3 and it was found that as the MDT was increased, the $DE_{8\%}$ was found to decrease. The MDT and $DE_{8\%}$ valued for F1L1 and F1L3 were found in the range of 3.58hr, 5.28hr and 83.3%, 74.10% respectively. Thus the formulation F1L3 showed sustained drug release.

Physicochemical characterization GG Matrix core and Tripled Layered Matrix Tablets

The prepared GG matrix core tablets were evaluated for physical parameters like hardness, thickness, friability, weight variation and drug content as shown in Table 2. The mean values for hardness of the layered matrix tablets of Tramadol HCL were in the range of 5.9±0.03 to 6.06±0.02 kg/cm^2. All the prepared tablets passed the friability test as the loss the tablet material were less than 1% in any case indicating that the tablets were of sufficient strength. All the layered matrix tablets satisfied the drug content as they contained 98.3±2.06% to 102.3± 3.51% of drug indicating uniform mixing of the GG, drug and other formulation excipients.

***In vitro* drug release studies of GG Matrix core and Tripled Layered Matrix Tablets**

The correlation coefficient (r^2) of the GG matrix tablet (F2) for first order release kinetics was found to be higher (0.959±0.02), when compared to that of zero order kinetics (0.730±0.04) indicating that the drug release from the matrix tablets followed first order kinetics (Table 2). However, in case of Triple layered matrix tablets, the 'r^2' values for zero order kinetics were found to be higher when compared than that of first order kinetics. Hence, it may be concluded that, a better controlled drug release can be achieved when a release retardant layer is formed on both sides of the matrix core. From the Table 2, it may be observed that, the 'r^2' values for 25mg and 50mg of EC layered on both the sides of the matrix core, the 'r^2' values are for zero order kinetics was found to be 0.799±0.01 and 0.845±0.05.In case of 75mg on both the sides of the EC layered matrix tablet the r value is 0.928±0.01. From this data, it can be noted that formulation F1L3 (EC of 75mg on both the surfaces) provides better control over the release than 25mg and 50 mg of the EC on both the surfaces of the matrix core. This could be attributed to the high thickness of the layer over the matrix core, shown in Figure 1b. The diffusional coefficient values obtained according to the model developed by Korsemeyer *et al* showed that matrix tablet followed Fickian diffusion and the Triple layered matrix tablets, followed non-Fickian diffusion, as the diffusion coefficient 'n' value was found to be less than 0.5 and greater than 0.5 respectively (Table 2). The correlation coefficient values for the Higuchi plots ranged from 0.982±0.02 to 0.990±0.02 for all the tablets i.e., both the matrix and the triple layered matrix tablets, indicating that the drug release from the tablets occurred by diffusion. Hence the results of the study indicated that the release of Tramadol HCL from the prepared matrix tablet followed first order kinetics via diffusion controlled mechanism and the triple layered matrix tablets followed zero order kinetics also via diffusion controlled mechanism. The MDT and $DE_{8\%}$ of the prepared formulations were calculated shown (Table 2) and it was found that as the MDT was increased, the $DE_{8\%}$ was found to decrease. The MDT and $DE_{8\%}$ valued for F23L1 and F2L3 were found in the range of 3.18hr, 4.38hr and 91.9%, 85.1% respectively. Thus the formulation F2L3 showed sustained drug release that was extended for over a period of more than 12hrs.

Physicochemical characterization XG Matrix core and Tripled Layered Matrix Tablets

The prepared XG matrix core tablets were evaluated for physical parameters like hardness, thickness, friability, weight variation and drug content as shown in table 3. The mean values for hardness of the layered matrix tablets of Tramadol HCL were in the range of 5.06± 0.01 to 6.10±0.02. All the prepared tablets passed the friability test as the loss the tablet material were less than 1% in any case indicating that the tablets were of sufficient strength. All the layered matrix tablets satisfied the drug content as they contained 98.3±2.06% to 100±1.97% of drug indicating uniform mixing of the XG with drug and other formulation excipients.

***In vitro* drug release studies of GG Matrix core and Tripled Layered Matrix Tablets**

The correlation coefficient(r^2) of the XG matrix tablet for first order release kinetics was found to be higher (0.991±0.04) when compared to that of zero order kinetics (0.934 ±0.03) indicating that the drug release from the matrix tablets followed first order kinetics (Table 3). However, in case of Triple layered matrix tablets, the 'r^2' values for zero order kinetics were found to be higher, when compared than that of first order kinetics. Hence, it may be concluded that a better controlled drug release can be achieved, when a release retardant layer is applied on the both sides of matrix core. From the Table 3, it may be observed that, the 'r^2' values for 25mg and 50mg EC layered on both the sides of the matrix core, 0.978±0.02 and 0.981±0.01. In case of 75mg EC layered on both the sides of matrix core, r^2 value obtained is 0.986±0.01. From this data, it can be noted that formulation F1L3 (75mg of EC on both the surfaces) provides better controlled over the release, than 25mg and 50mg of the EC layered matrix tablets This could also be attributed to the high thickness of the layers over the matrix core, shown in Figure 1c. The diffusional coefficient values obtained according to the model developed by Korsemeyer *et al* showed that matrix tablet (F3) followed Fickian diffusion and the triple layered matrix tablets followed non-Fickian diffusion, as the diffusion coefficient '*n*' value was found to be less than 0.5 and greater than 0.5 respectively (Table 3). It is evident from this data that, as EC layered on the matrix core retarded the drug release, improved zero order of the Tramadol HCL. From the above study, we may infer that EC 75mg layered on both the sides of matrix core provided better release to achieve zero-order profile than 25mg and 50mg layered on the matrix core. Then the drug release was sustained for more than 12hrs. The diffusional coefficient values obtained according to the model developed by Korsemeyer *et al* showed that matrix tablet followed Fickian diffusion and the Triple layered matrix tabletss followed non-Fickian diffusion, as the diffusion coefficient 'n' value was found to be less than 0.5 and greater than 0.5 respectively (Table 3). The correlation coefficient values for the Higuchi plots ranged from 0.971±0.03 to 0.981±0.04 for the prepared tablets i.e., both the matrix and the triple layered matrix tablets, indicating that the drug release from the tablets occurred by diffusion. Hence the results of the study indicated that the release of Tramadol HCL from the prepared matrix tablet followed first order kinetics via diffusion controlled mechanism and the triple layered matrix tablets followed zero order kinetics also via non-Fickian difusion mechanism. When 25mg of the EC was layered on both the surfaces of the matrix core formulation, the 'r^2' values obtained for F1L1, F2L1 & F3L1 were 0.871, 0.799 & 0.978. On further increasing the amount of EC 50mg on both sides of the matrix core, the corresponding 'r^2' values for F1L2, F2L2 & F3L2 were 0.964, 0.845&0.981. By employing the layer 75mg EC on both the sides of matrix core, the corresponding 'r^2' values for F1L3, F2L3 & F3L3 were 0.982, 0.928&0.986. As the releases retarding agent thickness is increased the release of the drug from the matrix core is delayed. It is evident from this data that, as the thickness of the layer increased, better linearization of the release can be obtained. The MDT and $DE_{8\%}$ of the prepared formulations were calculated shown in Table.3 and it was found that as the MDT was increased, the $DE_{8\%}$ was found to decrease. The MDT and $DE_{8\%}$ valued for F3L1 and F3L3 were found in the range of 12.32hr, 16.66hr and 56.8%, 63.5% respectively. Thus the formulation F3L3 showed sustained drug release, which was extended for over a period of more than 12hrs. The Viscosity of LBG was found to be more, when compared to GG and XG, but the retardation of drug release was higher with formulation containing LBG, it might due to might be due to degradation of LBG at high pH. Earlier it was reported from our laboratory that, LBG shows rapid rapid degradation and high erosion than other cellulose derivates.[20] Hence formulation containing XG in the matrix core shows more retardation, when layered with EC. After 6hrs, the EC layered was swelled and might formed uniform channels for media to diffuse into the matrix, to dissolve and to release the drug in a controlled manner. The first-order release rate constants obtained from F1L3, F2L3 and F3L3 formulations were 0.096±0.02h^{-1}, 0.083±0.01h^{-1} and 0.04±0.01h^{-1}, respectively. It signifies that with increasing the amount of EC on the matrix core, there is decrease in the first order rate constant. Formulation F3L3 showed, the calculated first release rate constant of 0.04h^{-1} Hence the F3L3 is an optimized formulation for the release of Tramadol HCL.

FT-IR Study

The IR spectra of the formulation were compared with the pure drug and formulation. All the spectra exhibited their specific characteristic peaks for C-H Aromatic (stretching) group at 3017.49cm^{-1}, C=C Aromatic (stretching) group at 1404.72cm^{-1}, C-N (stretching) group at 1161.78cm^{-1} and O-H (stretching) at 3345.87cm^{-1}. Based on the spectral data, there appears to be no possibility of interaction between Tramadol HCL and excipients used in the formulations.

Stability Studies

Stability studies were carried out by storing the formulations at 40±2^{0}C/75±5% RH for 6 months. At the end of testing period, the matrix tablets were observed for changes in physical appearance, analyzed for drug content and subjected to *in vitro* drug release studies. The triple layered matrix tablets F3L3 showed no significant change in dissolution pattern is shown in Figure 3.

Statistical analysis

Analysis of variance (single factor ANOVA) showed a significant differences ($P<0.05$) for the amount of Tramadol HCL released from the formulations (F3), and triple layered matrix tablets (F3L3)

CONCLUSIONS

Matrix forming natural polymers LBG, XG and GG alone in the matrix core could not prolong the Tramadol HCL release for more than 12hrs, predominately in a first order kinetics. The results indicated that a, layering with hydrophobic polymer EC controlled the THCL from the surfaces of matrix core, indicating that triple layer matrix tablets followed linear/zero order release profile. The release was extended for over a period of more than 12hrs. These dosage forms can be developed on large scale using layered tablet press.

Table 1: Formulae of Matrix and Triple Layered Matrix Tablets by using locust bean gum, gum ghatti and Xanthan gum in matrix core.

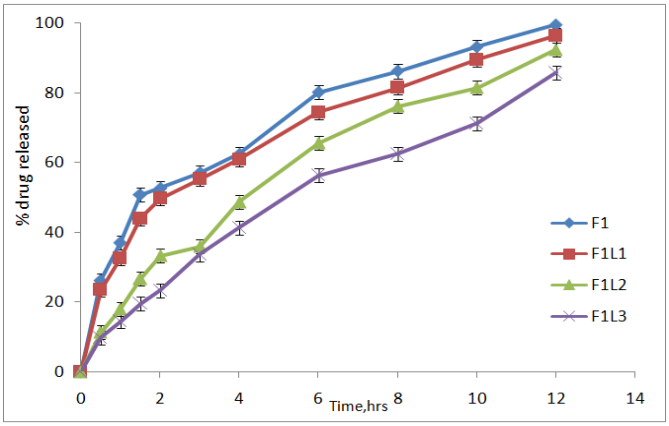
Formulations	F1	F1L1	F1L2	F1L3	F2	F2L1	F2L2	F2L3	F3	F3L1	F3L2	F3L3
Tramadol HCL	100	100	100	100	100	100	100	100	100	100	100	100
Locust bean gum	100	100	100	100	-	-	-	-	-	-	-	-
Gum ghatti	-	-	-	-	100	100	100	100	-	-	-	-
Xanthan Gum	-	-	-	-	-	-	-		100	100	100	100
Microcrystalline cellulose	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
PVPK30(5%w/v)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Top layer (EC)	-	25	50	75	-	25	50	75	-	25	50	75
Bottom layer(EC)	-	25	50	75	-	25	50	75	-	25	50	75
Total wt.(mg)	250	300	350	400	250	300	350	400	250	300	350	400

Table 2: Physical Parameters of Tramadol HCL Matrix and Triple Layered matrix tablets (Mean ± SD)

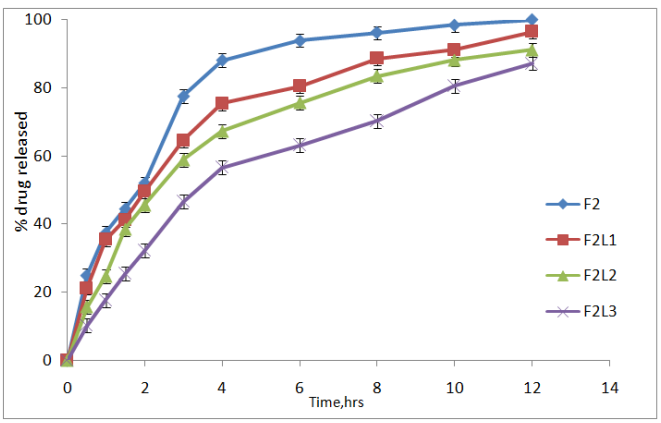
Formulation Code	Average wt of tablets (mg) n=3	Hardness kg/cm²n=3	Thickness (mm) n=3	Friability (%)n=3	Drug content (%) n=3
F1 (TH:LB)	250.1 ± 0.01	5.92± 0.10	3.02± 0.01	0.840± 0.015	102.3 ± 3.6
F1L1	301.2 ± 0.16	6.01± 0.02	3.12± 0.01	0.781± 0.036	103.2± 2.65
F1L2	350.2 ± 1.02	5.94± 0.05	4.01± 0.02	0.561± 0.025	98.15 ±2.25
F1 L3	400.1± 0.13	6.05± 0.03	5.02± 0.02	0.769± 0.015	101.0± 0.32
F2 (TH:GG)	250.0 ± 0.01	5.94± 0.03	3.01± 0.02	0.251± 0.025	98.6± 2.06
F2 L1	301.2 ± 0.16	6.10± 0.06	3.13± 0.02	0.365± 0.042	100.3± 0.91
F2 L2	351.1±1.02	6.04± 0.03	4.05± 0.03	0.602±0.001	101.0± 0.52
F2 L3	400.1± 0.13	5.93± 0.02	5.04± 0.03	0.868± 0.012	103.0± 2.5
F3 (TH:XG)	250 ± 0.13	5.06± 0.01	3.01± 0.01	0.420± 0.028	99.82 ±0.76
F3 L1	300.1± 1.10	6.01± 0.03	3.18± 0.06	0.807± 0.013	98.3± 2.06
F3 L2	350.1± 1.12	6.02± 0.03	4.06± 0.03	0.534± 0.001	98.5± 2.05
F3 L3	401.0± 1.68	6.10± 0.02	5.07± 0.03	0.562± 0.026	100± 1.97

Table 3: *In-vitro* dissolution kinetics, MDT and DE_8% of Tramadol HCL release from Matrix tablet and EC Triple layered Matrix Tablets (Mean±SD) n=3

Formulation codes	Zero order		First order		Higuchi	Peppas		MDT (hrs)	$DE_{8\%}$
	K_0	r^2	k^{-1}	r^2	r^2	*n*	k		
F1(TH:LB)	6.65±0.02	0.830±0.03	0.170±0.01	0.985±0.01	0.985±0.01	0.396±0.03	0.423±0.02	3.26±0.10	87.4±0.02
F1L1	6.87±0.01	0.871±0.02	0.103±0.02	0.991±0.02	0.986±0.03	0.438±0.01	0.471±0.01	3.58±0.36	83.3±0.16
F1L2	7.78±0.01	0.964±0.01	0.071±0.01	0.993±0.04	0.987±0.04	0.675±0.01	0.725±0.01	4.72±0.40	79.1±0.09
F1 L3	7.94±0.02	0.982±0.01	0.096±0.02	0.998±0.03	0.988±0.02	0.747±0.02	0.826±0.03	5.28±0.06	74.1±0.06
F2(TH:GG)	7.247±0.02	0.730±0.04	0.145±0.01	0.959±0.02	0.982±0.02	0.453±0.03	0.416±0.01	2.51±0.08	96.1±0.17
F2 L1	6.89±0.02	0.799±0.01	0.119±0.01	0.959±0.04	0.986±0.02	0.464±0.01	0.466±0.02	3.18±0.08	91.9±0.19
F2 L2	7.25±0.02	0.845±0.05	0.069±0.01	0.981±0.02	0.986±0.01	0.563±0.02	0.563±0.01	3.57±0.02	89.5±0.16
F2 L3	7.76±0.02	0.928±0.01	0.083±0.01	0.996±0.01	0.990±0.02	0.709±0.01	0.729±0.03	4.38±0.08	85.1±0.19
F3(TH:XG)	7.40±0.01	0.934±0.03	0.057±0.02	0.991±0.04	0.971±0.03	0.581±0.01	0.619±0.02	4.26±0.02	56.8±0.40
F3 L1	4.09±0.01	0.978±0.02	0.050±0.01	0.982±0.03	0.981±0.04	0.803±0.02	1.17±0.01	12.32±0.05	56.8±0.05
F3 L2	3.75±0.01	0.981±0.01	0.042±0.01	0.989±0.02	0.973±0.02	0.836±0.01	1.24±0.03	13.75±0.01	57.4±0.089
F3L3	3.20±0.01	0.986±0.01	0.040±0.01	0.981±0.02	0.974±0.03	0.827±0.01	1.29±0.01	16.66±0.04	63.5±0.19



(A)



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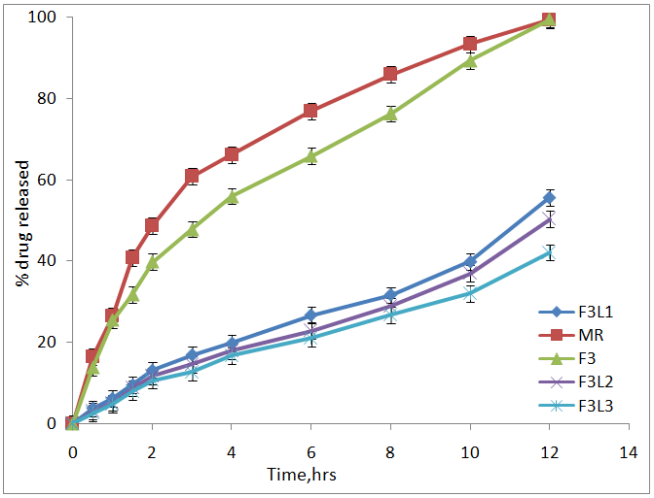
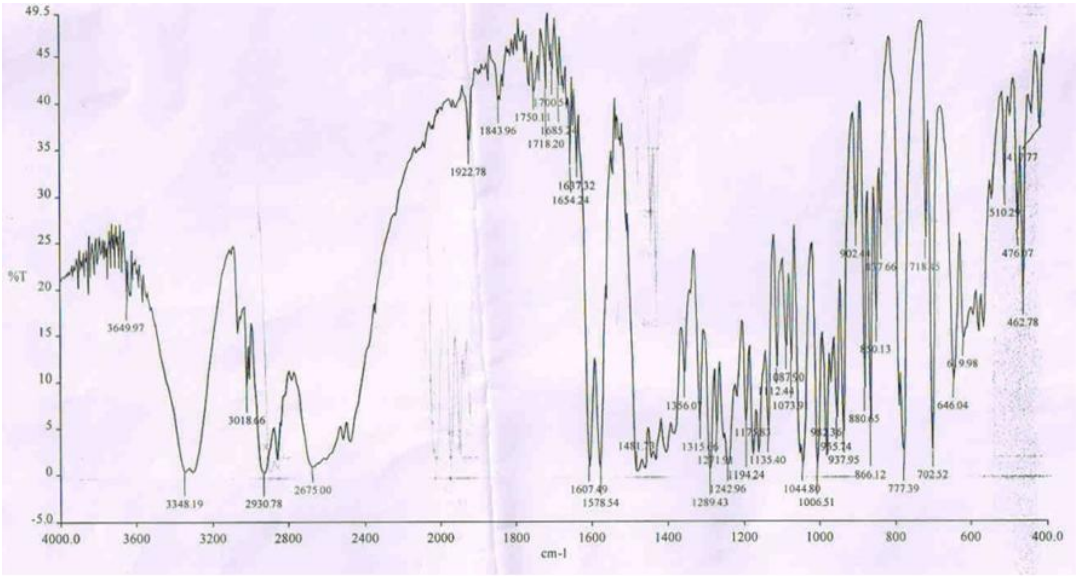
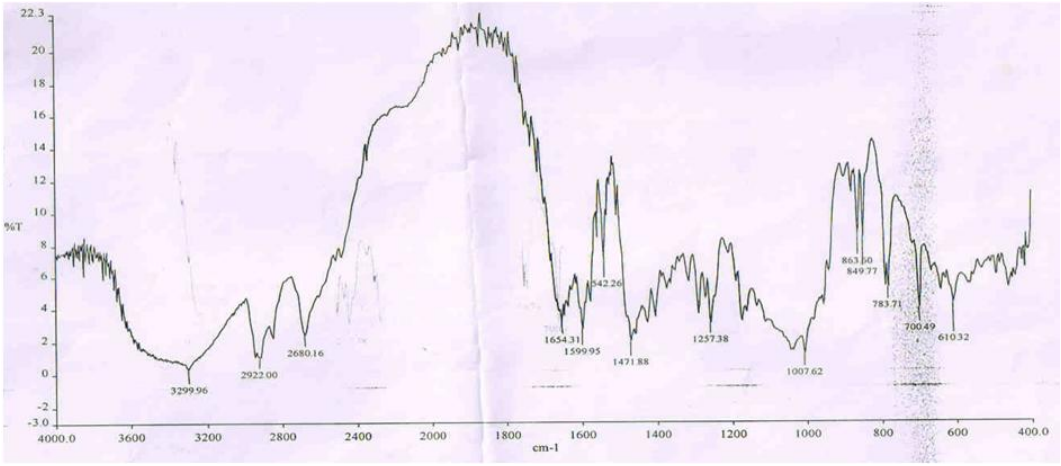


(C)

Fig. 1: Dissolution profiles of Tramadol HCL from matrix and triple layer matrix tablets conducted in pH 1.2 for 2 hrs and in pH 6.8 phosphate buffers remaining 10 hrs. a) F1, F1L1, F1L2 and F1L3 b) F2, F2L1, F2L2 and F2L3 c) F3, F3L1, F3L2 and F3L3.



(A)



(B)

Fig. 2: FT-IR graph of a) Tramadol HCL and b) triple layered matrix tablets (F3L3)

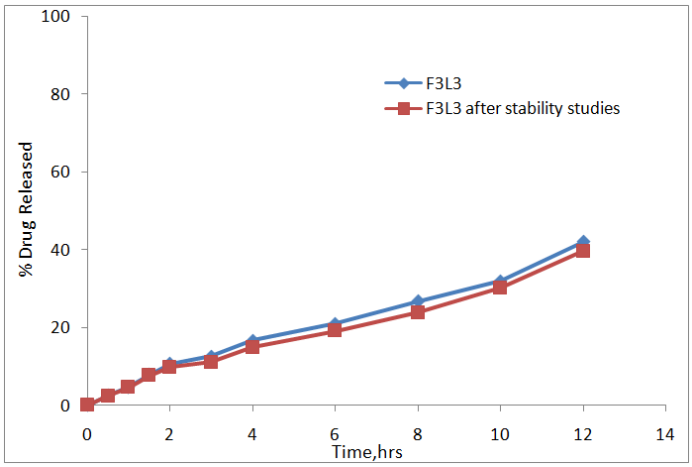


Fig. 3: *In vitro* dissolution profiles of triple-layer matrix tablets (F3L3) before and after storage at 40±2°C /75±5% RH for 6 months.

ACKNOWLEDGEMENTS

The authors are thankful to Dr. Reddy Labs, Hyderabad., India, Raj Enterprises, Mumbai, India, Krystal Colloids, Mumbai, India. Lucid gums Mumbai, India and Reliance cellulose products, Hyderabad, India. Reliance Cellulose Product, Hyderabad, India, for generously giving the samples of Tramadol Hydrochloride, Xanthan gum, Gum ghatti, Locust Bean gum and Micro Crystalline Cellulose and respectively. We are also grateful to the Principal and Management of SR College of Pharmacy, Warangal for their constant encouragement.

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