International Journal of Pharmaceutical Research and Development (IJPRD)
Platform for Pharmaceutical Researches & Ideas
www.ijprd.com

FORMULATION OF SUSTAIN RELEASE MATRIX TABLET OF TRAMADOL HYDROCHLORIDE USING HYDROPHOBIC POLYMERS

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ABSTRACT

To prepare oral sustained release matrix tablets of a highly water soluble drug Tramadol hydrochloride (TM), and to evaluate the effect of concentration of the hydrophobic polymer content and method of preparation on drug release. An inert matrix to sustain the release of TM was prepared using glyceryl behenate and glyceryl palmitostearate as a matrix forming agent. The matrix were prepared by either direct compression of a physical mixture of the drug and the matrix forming agent or by compression of granules prepared by hot fusion of the drug and the matrix forming agent. The hot fusion method was found to be more effective than compression of physical mixtures in retarding the release of the drug from the matrix. The tablets were prepared with different concentration of glyceryl behenate and glyceryl palmitostearate and also with combination of both. The tablets were evaluated for precompression and post compression evaluation. Drug polymer interaction was determined by FT-IR spectroscopy and the release of matrix tablet was studied using USP II dissolution apparatus. The drug release was decreased with increasing concentration of hydrophobic materials. Glyceryl behenate was found to be more effective to retard the drug release as compared to glyceryl palmitostearate. The optimized batch was selected on the basis of comparison with marketed SR product using similarity (F2) and dissimilarity factor (F1). The drug release mechanism form the formulation was by Fickian diffusion as the hydrophobic polymer are not soluble even in acidic and alkaline medium.

KEYWORDS : *Tramadol Hydrochloride, Hydrophobic polymers, Melt granulation etc.*

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INTRODUCTION

A sustained-release dosage form is defined as "any drug or dosage form modification that prolongs the therapeutic activity of the drug" [1]. The primary objectives of sustained drug delivery are to ensure safety and enhancement of efficacy of drug with improved patient compliance. This delivery system is increasingly being used in the treatment of acute and chronic diseases as they maintain the concentration of drug in plasma above the minimum effective concentration and below the minimum toxic level for an extended period of time. Thus, sustained drug delivery results in optimum drug therapy with reduced frequency of dosing and side effects [2].

Tramadol Hydrochloride (TM). TM a centrally acting opioid analgesic is used in severeacuteorchronic pains [3].Tramadol is an aminocyclohexanol derivative or 4-phenylpiperidine analogue of codeine. Its analgesic effect is mediated through norepinephrine reuptake inhibition [4]**.** Its mean elimination half-life is ~ 6 hrs and require dosing every 6 hrs in order to maintain optimal relief of chronic pain. It offers several therapeutic advantages over other analgesics, such as good oral bioavailability and long elimination half-life (5–7 h). Despite the long elimination half-life, TM is prescribed 3–4 times a day [5]. Frequent dosing schedule often leads to decreased patient compliance, increased incidence of side effects and tolerance development, especially, in long-term use in conditions like arthritis, osteoarthritis, arthralgia, postoperative surgical pains, etc. It seems that there is a strong clinical need and market potential for a delivery system that can deliver TM in a controlled manner [6].

Waxy materials have major applications in sustained release systems, especially for highly water-soluble drugs. Examples of waxy material include hydrogenated oils, glyceryl stearates, fatty alcohols and microcrystalline wax. Such material provide several advantages ranging from good stability of varying pH values and moisture levels to well established safe application in humans. Matrix delivery systems utilizing waxy materials usually employ a core of drug embedded in the wax or a compressed physical blend of drug and matrix forming agent. As the system passed through the gastrointestinal tract (GIT), the active ingredients is slowly released and absorbed [7]. Since they are water insoluble and non- swellable, waxy materials have been introduced to eliminate the effects of food present in the GIT on the matrix tablets. These effects range from shearing the hydrated polymer gel layer leading to 'dose di=umping' to blocking the pores of matrix and inhibiting the drug release [8].

Glycerides are a family of excipients which have generated considerable interest in the preparation of oral dosage forms. Some glycerides such as glyceryl palmitostearate (Precirol ATO 5), Glyceryl behenate (Compritol 888 ATO) can be used for the preparation of sustained release dosage forms. The esterification of glycerol by long chain fatty acid gives them a pronounced hydrophobic character with a low HLB value. Glyceryl behenate (Compritol 888 ATO) is a waxy material, originally introduced as a lubricant in compressing tablets, which has recently had a wide application as a sustained-release agent. It is commonly used as a lubricant and binding agent for tablets in the concentration of 1-3% and a sustained release excipients in concentrations above 10%. A recent study by Barthelemy and coworkers investigated that use of glyceryl behenate as a hot melt coating agent to prolong the release of theophylline.

Melt granulation is a solvent-free process which involves the use of a substance that melts at a relatively low temperature. This substance can be added in the molten form over the substrate or in the solid form, which is then heated above its melting point. The substance acts as a liquid binding agent, and the technique does not require the use of organic solvents. Moreover, in melt granulation drying is not necessary and thus, the process is less consuming in terms of time and energy compared to other methods

The objective of the study was to prepare oral sustained release tramadol HCl matrix tablets utilizing a simple technique that uses glyceryl

behenate and glyceryl palmitostearate as a matrix-forming agent and which would provide an extended duration of therapeutic effect with minimum potential for side effects.

MATERIALS AND METHODS:

Materials:

Tramadol Hydrochloride was obtained from (Sun Pharmaceutical Industries Ltd., Maharashtra, India) as a gift sample,glyceryl palmitostearate (Precirol ATO 5) and glyceryl behenate (Compritol 888 ATO) were obtain from Gattefosse Corp, France as a gift sample. Concentrated hydrochloric acid, sodium hydroxide and potassium dihydrogen phosphate were also obtained free of charge from Fine Chemicals Ltd, Mumbai, India.

METHODS:

Preparation of matrices by hot fusion method:

Polymers (Glyceryl behenate/ Glyceryl palmitostearate/ combination of glyceryl behenate and glyceryl palmitostearate) were melted in continuous stirring in a porcelain dish on a water bath maintained at 75º C. The Drug (Tramadol Hydrochloride) was added with continuous stirring. Then the molten mass was allowed to cool down and solidify. TM was present in its solid form within the molten mass. The mass was ground and screened, and the granules retained on 1.25 mm sieve were used. These granules were compressed into flat faced tablets a KBr pellet press at a force of 1 ton. The Formulations compositions are shown below in Table1.

Table 1 Formulation composition of TM in matrix system

Sr. No.	Formulation code	Drug : polymer ratio	Total weight
1	MG1	TM: Comp (1:1)	200
2	MG2	TM: Comp (1:2)	300
3	MG3	TM: Comp (1:3)	400
4	MG4	TM: Prec (1:1)	200
5	MG5	TM: Prec (1:1)	300
6	MG6	TM: Prec (1:1)	400
7	MG7	TM: Comp:Prec (1:1:1)	300
8	MG8	TM: Comp:Prec (1:2:1)	400
9	MG9	TM: Comp:Prec (1:1:2)	400
10	DC1	TM: Comp:Prec (1:2:1)	400

TM: Tramadol Hydrochloride, Comp: Compritol 888ATO, Prec: Precirol ATO 05

Preparation of matrices by direct compression of physical mixtures:

The drug, Glyceryl behenate and glyceryl palmitostearate (Formula as table 1 DC1) were mixed in mortar for 10 min and compressed into flat faced punch.

Precompression evaluation:

Compatibility study by Fourier Transform Infra Red (FTIR) spectroscopy:

Chemical interaction between the drug and the polymeric material, if any, during the preparation of the tablets was studied by using Fourier Transform Infrared Spectroscopy (FTIR). Infrared spectrum of the drug, meltable binders and granules were recorded using a FTIR (model 4100 type A, Perkin-Elmer, Norwak, CT, USA) spectrometer using KBr pellets (400-4000-1) with a scanning speed of 2 mm/sec with normal slit.

Angle of repose:

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the granules. The granules were allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation 1.

$$\emptyset = \tan^{-1} \left(\frac{h}{r}\right) \quad \text{.....1}$$

where, θ= angle of repose

h= height of cone, r= radius of the cone base

Bulk density:

Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 10 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 100 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations 2 and 3 respectively.

$$LBD = \frac{Weight\ of\ powder\ blend}{Untaped\ volume\ of\ packing} \text{.....2}$$

$$TBD = \frac{Weight\ of\ powder\ blend}{Taped\ volume\ of\ packing} \text{.....3}$$

Compressibility Index:

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. Carr's Index were calculated using the formula 4.

Carr's Index

$$(\%) = \frac{\langle (TBD - LBD) \times 100 \rangle}{TBD} \text{.....4}$$

Where, TBD= Tapped bulk density

LBD= Loose bulk density

Hausner's Ratio:

Hausner's Ratio is the ratio of bulk volume to tapped volume or tapped density to bulk density and calculated by following formula 5.

Hausner's Ratio = V_0/V 5

Where, V_0 = Bulk volume

V= Tapped Volume

Post compression evaluation:

Thickness:

Thickness of tablets was determined using Vernier caliper. Five tablets from each batch were used, and average values were calculated. The thickness was measured by placing tablet between two arms of the Vanier calipers.

Drug content:

Drug content was determined by ten tablets were weighed and powdered. A quantity of powder equivalent to 50 mg of TM was taken. It was shaken with 70 ml of water for 15 min. and then diluted to 100 ml with water. It was filtered through Whatman filter paper no. 41. One ml of this solution was transferred to 10 ml volumetric flask and final volume was made 10 ml. Absorbance of the resulting solution was measured at 271 nm. The drug content was determined by referring to the calibration curve.

Hardness:

For each formulation, the hardness of 5 tablets was determined using the Pfizer hardness tester. The value was noted in kg/cm^2.

Friability:

The friability of the tablets was measured in a Roche friabalator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_0) approximately 6.5 gm are deducted in a drum for a fixed time 4 min (100 revolutions) at 25 rpm, dropping the tablets to a distance of 6 inches in each revolution and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation 6. The weight loss should not be more than 1.

$$\% \text{ Friability} = \frac{Wo - W}{Wo} \times 100 \text{ ----------6}$$

***In-vitro* drug release studies of TM matrix tablets:**

The In-vitro dissolution study of TM matrix tablets was determined spectrophotometrically using USP dissolution apparatus (Electrolab, TDT-08L). The 900 ml of 1.2 pH was used as dissolution media for 2 h followed by 22 h study in 6.8 pH phosphate buffer. The pH of the medium was adjusted to 6.8 after 2 h by adding 2.4 g ofSodium hydroxide and 3.38 g of Potassium dihydrogen phosphate dissolved in 5 ml water. Temperature was maintained constant at 37 ± 0.5 °C. The paddle rotation speed was kept at 100 rpm. At predetermined time interval 5 ml sample was withdrawn, filtered, suitably diluted and assayed at 271 nm by UVspectrophotometer (Shimadzu 1800). All the parameters were run 3 times (n=3)

The graphs of times vs. % cumulative release were plotted. Also the in-vitro drug release study for the marketed tablet was conducted.

Kinetics of the drug release

To determine the volume of regression coefficient (r2) and mechanism of drug release form the formulation, the cumulative release data were fitted to models representing zero-order (Cumulative percentage drug released v/s time, Eq. 7), first-order (log cumulative percentage drug retained v/s time, Eq. 8), Higuchi's square root of time (Cumulative percentage drug released v/s square root of time, Eq 9) and Korsemeyerpeppas double log plot (log of fraction of drug released v/s log time, Eq 10).

$$Mt = M_0 + k_0 t \text{----------7}$$

$$\text{In } Mt = \text{In } M_0 + k_1 t \text{----------8}$$

$$Mt = M_0 + k H t^{1/2} \text{----------9}$$

$$Mt / M\square = ktn \text{----------10}$$

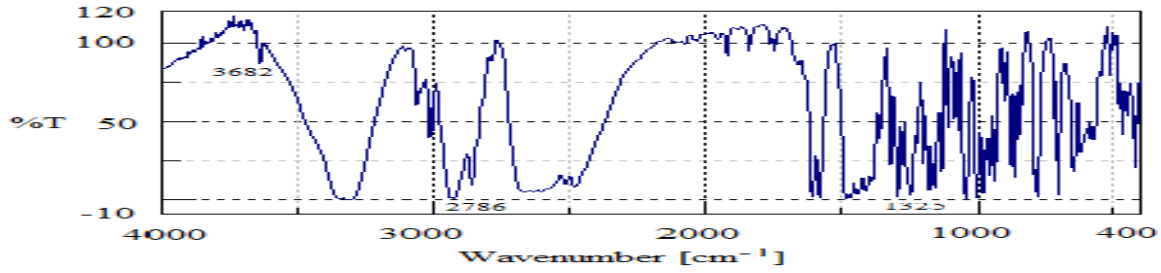
Where Mt is the cumulative amount of drug released at any time, t and M_0 is the dose of the drug incorporated in the delivery system. k0, k1 and kH are rate constants for zero-order, first order and Higuchi models, respectively.

RESULTS AND DISCUSSION:

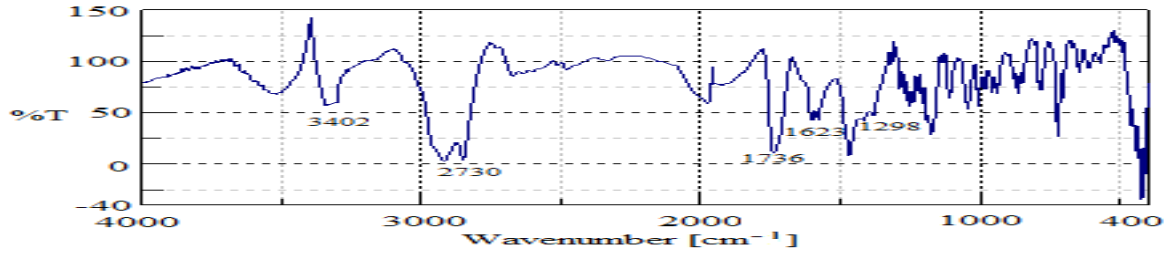
Compatibility study:

Chemical interaction between the drug and the polymeric material, if any, during the preparation of the tablets was studied by using Fourier Transform Infrared Spectroscopy (FTIR).

(a)



(b)



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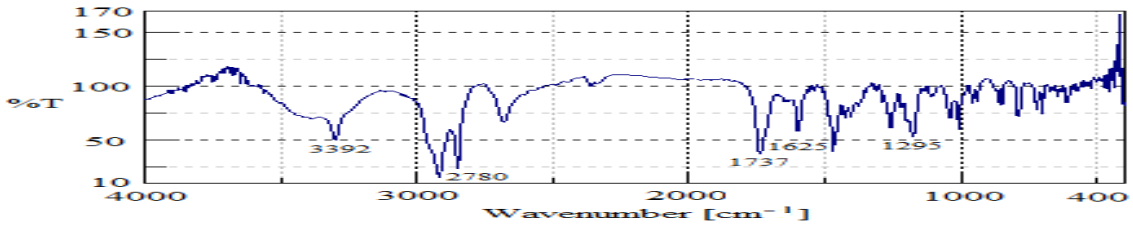

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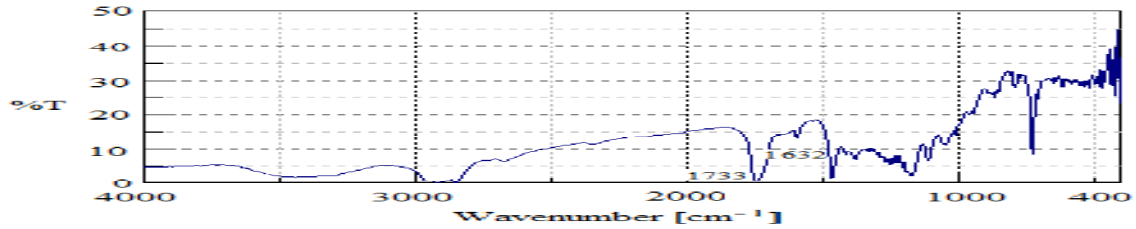

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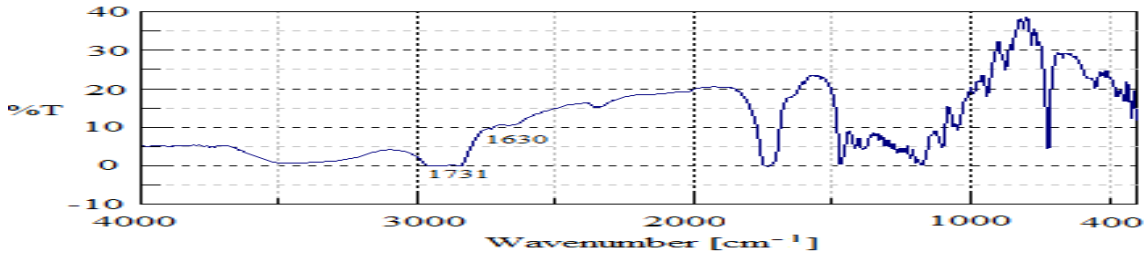


Figure 1 IR spectrum of (a) TM (b) TM: Compritol 888 ATO (c) TM: Precirol ATO 5 (d) Compritol 888 ATO and (e) Precirol ATO 5

From IR spectroscopic study, it was found that there was no evidence of interaction between drug and polymers.

Pre compression evaluation:

Various micromeritics properties of the granules from each batch are summarized in Table 2.The granules of various formulations containing drug and meltable binders were evaluated for the angle of repose, Loose Bulk Density (LBD), Tapped Bulk Density (TBD), Carr's index, haunsar ratio. These In Process Quality control (IPQC) parameters were evaluated for the flow properties and the compressibility of granules.

Angle of repose and compressibility index:

The angle of repose for all formulations fell within the range of 16- 20^0 indicating excellent flow properties. The angle of repose is a characteristic of internal friction or cohesion of the particles. If the value of angle of repose is high, powder is cohesive and if angle of repose low powder is non cohesive

These values for angle of repose (< 20) indicated excellent flow properties of granules and this was further supported by lower compressibility index values. Compressibility index for all formulations were found to be in the range of 7.50 to 12.67 %. Generally, compressibility index values up to 15% results in good to excellent flow properties.

Loose bulk density and tapped bulk density:

The bulk density of a powder depends primarily on particle size distribution, particle shape and the tendency of particle to adhere together. The values for LBD and TBD were found to be in the range of 0.57 to 0.74 g/cm3 and 0.62 to 0.80 g/cm3 indicating good packing capacity. These values may further influence properties such as compressibility and tablet dissolution.

Haunser's ratio:

Haunser's ratio of all formulation found to be in the range of 0.87 to 0.94 indicated that all formulation having excellent flow property

Table 2: Evaluation of micromeritics properties of the granules

Formulation code	Angle of repose	LBD g/cm^3	TBD g/cm^3	Carr's index (%)	Hausner's Ratio (%)
MG1	18.00	0.58	0.66	12.12	0.88
MG2	19.57	0.68	0.76	10.52	0.89
MG3	16.17	0.57	0.64	10.93	0.89
MG4	19.15	0.74	0.80	7.50	0.93

MG5	17.35	0.66	0.74	10.80	0.89
MG6	16.38	0.60	0.66	9.09	0.91
MG7	19.44	0.62	0.68	8.80	0.91
MG8	18.43	0.58	0.62	6.45	0.94
MG9	16.69	0.57	0.62	8.06	0.92
DC1	18.70	0.62	0.71	12.67	0.87

Post compression evaluation:

Tablets of each formulation were evaluated for parameters such as Thickness, diameter, Drug content, Hardness and Friability given in Table 3.

Thickness:

As there was no much variation in thickness of tablets in each formulation, it shows that granules and powder blends were consistent in particle size and uniform behavior during compression process.

Hardness:

The hardness of tablet was measured on Pfizer hardness tester. The hardness was in range of 5.2 ± 0.10 to 6.5 ± 0.30 kg/cm^2. As per as hardness is to be concern MG1, MG2, MG4 and MG5 showed hardness in the range between 5.2 ± 0.10 to 5.5 ± 0.10 kg/cm^2, where as in case of formulations MG3, MG6, MG7, MG8, MG9 and DC1 hardness slightly increases in the range of 5.9 ± 0.10 to 6.5 ± 0.30 kg/cm^2 is may be due to increase in concentration of lipophilic binder. Increase in meltable binder content increase the interparticulate bonding during compaction which results in increase in crushing strength of tablets. The hardness of all formulations matrices were within the standard range i.e. not less than 5 kg/cm^2.

Friability:

Friability was found to be 0.68 ± 0.03 to 0.92 ± 0.03%. As friability was below 1 % tablets in each formulation can withstand the mechanical shocks. All the parameters were run 3 times (n=3). The difference in mean of thickness, diameter, weight variation, drug content, hardness and friability between batch series 'MG' and batch 'DC1' was significant ($p < 0.05$).

Drug content:

The tablets were analyzed for potency. The drug content uniformity was in range of 95 to 100% showing uniform distribution of drug in matrix.

Table 3: Post compression evaluation of TM matrix tablet

Formulation code	Thickness mm ± SD	Hardness (Kg/cm^2) ± SD	Friability (%) ± SD	Tablet Weight (mg) ± SD	Drug content (%) ± SD
MG1	1.260±0.06	5.2±0.10	0.81±0.02	197.55±0.64	96.87±0.40
MG2	1.972±0.12	5.5±0.10	0.92±0.03	297.50±0.70	96.18±0.84
MG3	2.648±0.08	6.2±0.10	0.71±0.04	395.40±0.52	97.50±0.52
MG4	1.342±0.08	5.2±0.10	0.89±0.06	196.67±0.57	95.35±0.82
MG5	1.972±0.13	5.4±0.17	0.81±0.05	296.65±0.52	97.19±1.13
MG6	2.647±0.08	5.9±0.10	0.68±0.03	396.80±0.53	96.30±0.39
MG7	2.018±0.15	6.0±0.10	0.83±0.09	295.98±0.89	98.35±0.37
MG8	2.676±0.04	6.4±0.06	0.75±0.07	395.94±1.00	98.76±1.32
MG9	2.640±0.05	6.2±0.06	0.74±0.12	396.94±1.66	99.21±0.56
DC1	2.663±0.32	6.5±0.30	0.87±0.06	398.01±0.68	97.13±0.82

***In-vitro* drug release study of TM matrix tablets:**

The *in-vitro* drug release characteristics were studied in 900 ml of pH 1.2 was used for 2 h followed by 22 h study in pH 6.8 phosphate buffer using USP type II dissolution apparatus. The theoretical release profile calculation is important to evaluate the formulation with respect to release rates and to ascertain whether it releases the drug in predetermined manner as per shown in microspheres. According to theoretical calculation

the formulation should release 26.51 mg in 1 hour as a loading dose and 3.51 mg per hour for up to 24 h.

The drug release profile for TM tablet is shown in table Figure 2. It was observed that TM release was slow and spread over 24 hours and depends on polymer concentration. The rate of release decreased as the concentration of the carrier was increased. This may be due to low permeability of polymer to the drug or slower penetration of dissolution medium in waxy materials i.e. increasing the ratio of drug: lipophilic binders from 1:1 to 1:3 resulted in decreasing release of drug.

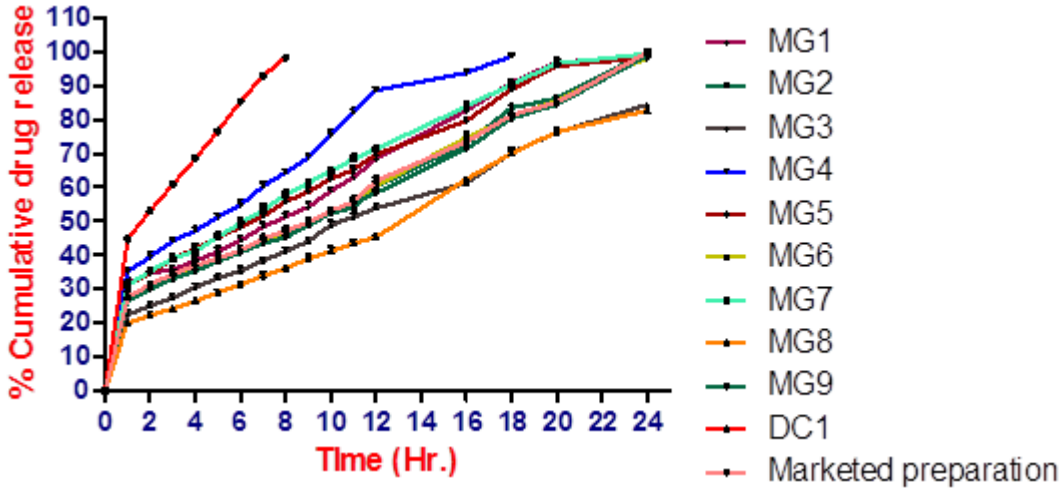


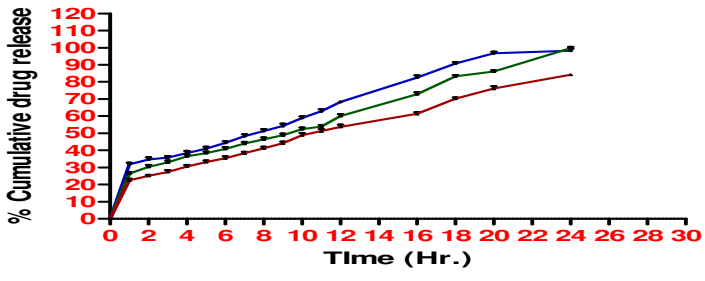
Figure 2: In Vitro dissolution of MG1 to MG9, DC1 and marketed preparation

Effect of type of lipophilic binder on release rate of TM:

The effect of type of lipophilic binder on the release of TM shows in figure 3. From this it can be observed that for all the matrices drug release is inversely proportional to level of rate retarding matrix former present in the matrix system i.e. the rate and extent of drug release decrease with increase in total lipid content of matrix

Matrix tablet of TM prepared either with Compritol 888 ATO or Precirol ATO effectively retarded the release of drug. It was found that release of drug from Compritol 888 ATO gets more retarded than that from Precirol ATO 5 and also it was found that matrix tablet with combination of Compritol 888 ATO and Precirol ATO 5, most effectively retarded the release of drug. In formulation MG8 Drug: Compritol 888 ATO: Precirol ATO 5 (1:2:1) proportion shows 82.63% drug release at the end of 24 h. it may be due to higher lipophilicity offered by combination of lipophilic binder than that of lipophilic binder when used alone.

Among the lipophilic agents, Compritol 888 ATO was found to be especially effective for several reasons: its high melting point (65 to 77^{0}C) avoids occurrence of sticking to punches during tabletting operation, it allows for maintenance of tablet integrity even after complete dissolution of drug and release of a drug can be easily modulated by varying its concentration in matrix tablet.

TM: Compritol 888 ATO	

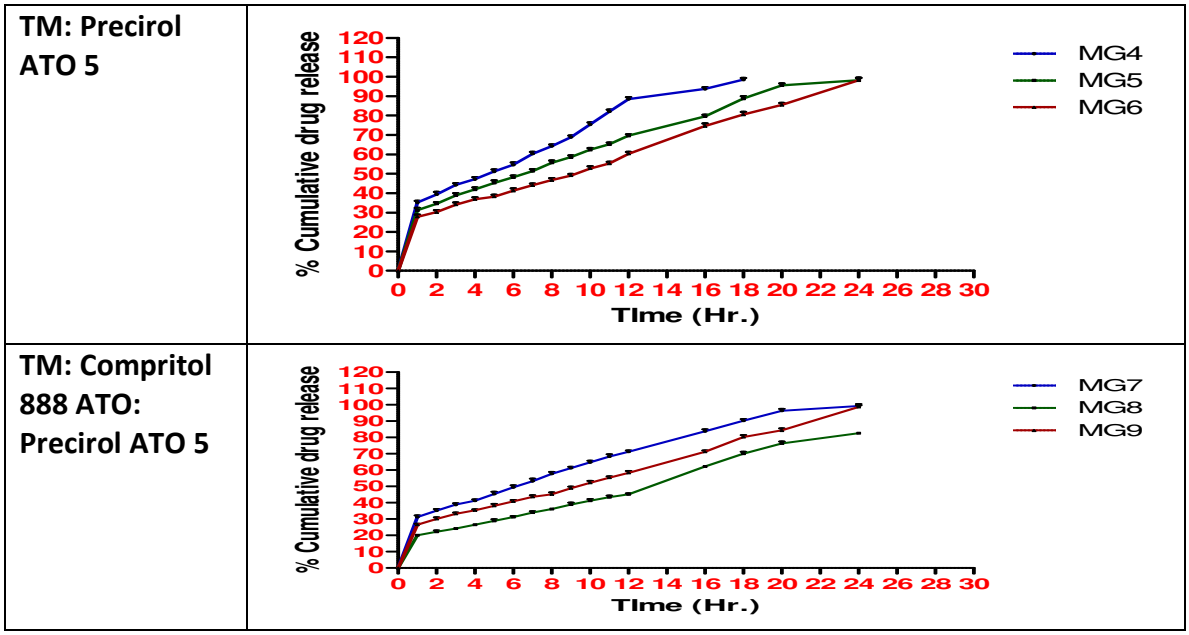


Figure 3: Effect of type of lipophilic binder on release rate of TM

Effect of method of preparation on release rate of TM:

With the aim of studying effect of method of preparation of sustained release tablets on drug release properties of TM, the matrices were prepared by two methods i.e.physical mixtures by direct compression and melt granulation. From the above *in vitro* data said lipophilic binders for ratio of 1:2:1 drug: meltable binder (MG8) which was showed more retard drug release and was selected for effect of method of preparation. Figure 4 shows comparative release profiles of matrix tablet prepared by direct compression of physical mixtures and matrix tablet prepared by compression of granules prepared by melt granulation. The release was higher from the DC1 formulation matrix tablets made by direct compression of physical mixtures as compared to MG8 formulation matrices prepared by compression of granules by melt granulation.

The result attributed to this formation of coating of lipophilic binder over drug particles is more uniform in melt granulation technique than matrix tablet prepared by direct compression

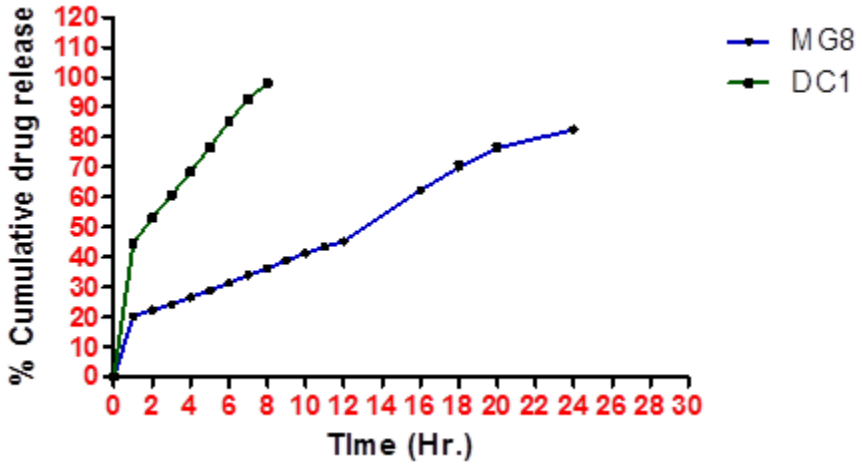


Figure 4: Comparative release profile of tablet made by direct compression (DC1) and melt granulation (MG8)

Kinetics of drug release:

Analysis of the release data as per zero and first order kinetics models indicated that TM release from Compritol and Precirol matrix tablets followed zero order kinetics. Correlation coefficient (R^2) values in the zero order model were higher than those in first order model. (Table 4).When the release data were analyzed as per peppas equation, the release exponent 'n' was <0.5 (Table 5) with all the batches of TM indicating Fickian diffusion as the drug release mechanism from these microcapsules. To evaluate drug release mechanism from the Compritol and Precirol matrix tablet plot of the percent released versus square root of time (Higuchi's model) were constructed. The plot were found to be linear with correlation coefficient values higher than 0.9241. These plots indicated that the drug release mechanism from the Compritol and Precirol matrix tablets were diffusion controlled. As the Compritol and Precirol is insoluble in both acidic and alkaline fluids the mechanisms of dissolution and erosion of the tablet are not applicable [9,10,11].

Table 4: Regression coefficients of different kinetics models for TM matrix tablet

Formulation code	Zero order (r^2)	First order (r^2)	Higuchi kinetics (r^2)	Peppas Equation (r^2)±SD
MG1	0.9819	0.8873	0.9440	0.8927
MG2	0.9938	0.9284	0.9391	0.9143
MG3	0.9964	0.9627	0.9638	0.9378
MG4	0.9716	0.8928	0.9651	0.9394
MG5	0.9886	0.8934	0.9747	0.9482
MG6	0.9960	0.7958	0.9436	0.9100
MG7	0.9835	0.8675	0.9813	0.9541
MG8	0.9865	0.9457	0.9241	0.8991
MG9	0.9962	0.7490	0.9418	0.9148
DC1	0.9981	0.8809	0.9849	0.9727
Marketed Preparation	0.9959	0.6490	0.9437	0.9141

Table 5: Release characteristics of TM Matrix tablet

Formulation code	K_0 (mg/h)	K_1 (h^{-1})	'n' in peppas equation
MG1	3.628	0.153	0.408
MG2	3.461	0.171	0.428
MG3	2.989	0.066	0.444
MG4	4.625	0.194	0.391
MG5	3.478	0.143	0.396
MG6	3.382	1.121	0.414
MG7	3.565	0.168	0.406
MG8	3.072	0.066	0.478
MG9	3.375	0.125	0.421
DC1	10.290	0.416	0.390
Marketed Preparation	3.388	0.156	0.412

CONCLUSION:

The study showed that glyceryl behenate (Compritol 888 ATO) was appropriate waxy sustained release polymer as compared to glyceryl behanate (Precirol ATO 5) for sustained release of water soluble drug such as TM. As per method of

preparation matrix tablet prepared by melt granulation technique were far superior to those prepared by direct compression of physical mixture [13].

ACKNOWLEDGEMENT:
The authors are grateful to Sun Pharmaceutical Industries, Gattefosse Corp, France and Fine chemicals, Mumbai for the gift samples of Tramadol Hydrochloride, chitosan, Compritol, Precirol, Concentrated hydrochloric acid, sodium hydroxide and potassium dihydrogen phosphate respectively.

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