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FORMULATION AND EVALUATION OF TRAMADOL POROUS TABLETS

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ABSTRACT

The present research work was aimed to develop a porous tablet of tramadol using various polymers. The formulation was optimized by using various concentrations of the disintegrants and other excipients. Menthol was used as the sublimating agent. Absorption maxima was determined to be 272nm and the calibration curve was plotted using the absorbance values of various concentration of the drug. Prior to tablet making, the formulation bled was subjected to preformulation studies which were found to be within the acceptance range indicating the powder has good flow properties. Among all the eight formulations, sixth formulation (F6) having cross carmelose in the concentration of 25mg has the highest release rate where 100.26% of the drug was release within 30 mins similar to eighth formulation but sixth formulation was considered as optimized due to low sublimating agent concentration. Moreover, FT-IR spectrum obtained showed no drug-excipient incompatibility used in preparing the formulations. Therefore, the optimized formulation F6 can be employed for scale up process as the method is simple, easy and cost effective and hence can be used during large scale production.

KEYWORDS: Porous tablet, tramadol, absorbtion maxima, preformulation studies, post formulation studies, stability.

INTRODUCTION

Tramadol is chemically (1R,2R)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol with the molecular formula C16H25NO2 and molecular weight of 263.381g/mol.[1] It is a synthetic analogue of codeine[2] which has significantly lower affinity for opioid receptors than codeine. It is a narcotic analgesic which acts as selective weak OP3-receptor agonists.[3-5] It exists as a racemic mixture and the mean peak plasma concentration occurs two hours after its oral administration.[6] It is used to treat postoperative[7-9], dental[10], cancer[11-12] and acute musculoskeletal pain[13] and as an adjuvant to NSAID therapy in patients with osteoarthritis.[14-15] Literature study reveals various formulations of tramadol and its evaluation.[16-22] However, there was no study in the preparation of tramadol porous tablet. Therefore, the present study was aimed to formulate a porous tablet of tramadol using direct compression method with menthol as sublimating agent and evaluate their pre and post formulation parameters.

MATERIALS AND METHODOLOGY

Materials and Instrumentation

Tramadol standard drug was obtained as a gift sample from Chandra labs, Hyderabad, India. Cross povidone, cross caramelose and sodium starch glycolate were purchased from MYL CHEM, Mumbai, India. Micro crystalline cellulose, magnesium stearate and talc were obtained from S.D Fine chem. LTD, Mumbai where as Avicel pH 102 and menthol were obtained from FMC Biopolymer and Fine chem laboratories respectively.

Drug excipients compatibility studies were studied using FTIR spectrophotometer of Per Kin Elmer, USA and a double beam UV-Visible spectrophotometer was used to obtain the absorbance values at 272nm. Single punch compression machine of Cadmach was used to formulate tablet. Post formulation studies were performed using Schleuniger hardness tester, friability test apparatus and bulk density apparatus of Electrolab. Dissolution test was performed using tablet dissolution USP apparatus –I (Basket Method) of Distek, Dissolution system 2100C.

Formulation of Tramadol porous tablets by direct compression method

Porous tablets of Tramadol were prepared by direct compression method employing menthol as sublimating agent. All the ingredients were weighed accurately. The tramadol drug was mixed with the release rate enhancing disintegrants and other excipient in ascending order of their weight except magnesium stearate. The powder mix was blended for 20 min to have uniform distribution of drug in the formulation. Then, magnesium stearate was added and mixed for not more than 1 min (to ensure good lubrication.) About 200 mg of the powder mix was weighed accurately and fed into the die of single punch machinery and compressed using 8 mm flat- surface punches. The hardness of the tablets was adjusted at 4-6 kg/cm2 using a Monsanto hardness tester. Table no: 1 shows the composition of the tablet formulations.

Table No: 1 Composition Of The Tablet Fromulations F1-F8.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Tramadol	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg
SSG	10	--	--	--	--	--	--	--
CCS	--	10	--	15	20	25	20	25
CP	--	--	10	--	--	--	--	--
Talc	5	5	5	5	5	5	5	5
Menthol	10	10	10	10	10	10	15	15
MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Mg.stearate	5	5	5	5	5	5	5	5
Total weight	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg

EVALUATION OF TABLETS

To design tablets and later monitor tablet production quality, quantitative evaluation and assessment of tablet chemical, physical and bioavailability properties must be made. The important parameters in the evaluation of tablets can be divided into physical and chemical parameters.

Physical appearance

For consumer acceptance, the general appearance of tablets, its visual identity and overall elegance is essential which can be controlled by measurement of number of attributes such as tablet size, shape, colour, presence or absence of odour, taste, surface texture and consistency of any identification marks.

Hardness test

It is tested by observing the force required to break a tablet in a diametric compression. Hardness of the tablet is determined by Stock's Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moves along the gauze in the barrel fracture.

Tablet Thickness

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by Vernier Calipers scale. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ±5%. In addition, to facilitate packaging, thickness must be controlled.

Friability

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the friabilator, rotating at 25rpm for 4min. The difference in the weight is noted and expressed as percentage. It should be preferably between 0.5 to 1.0%.

%Friability = (W1-W2)/W1 X 100

Where, W1= weight o f tablets before test

W2 = weight of tablets after test

Weight variation of Tablets

All the tablets of a particular batch should be uniform in weight. Any weight variation that is observed, it should fall within the prescribed limits.

Twenty tablets were taken randomly and weighed accurately.

The average weight was calculated by:

$$Average\ weight = weight\ of\ 20\ tablets/20$$

Disintegration test

Disintegration time is considered to be one of the important criteria in selecting the best formulation. Several methods were proposed, developed and followed at their convenience to achieve correlation between disintegration time in-vitro and in-vivo. One tablet was placed into each tube and the assembly was suspended into the 1000ml beaker containing water maintained at 37±2oc and operated the apparatus for 15 minutes. The assembly was removed from the liquid and the tablets were observed. If one or two tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not less than 16 of the total of 18 tablets tested are disintegrated.

Preparation of calibration curve

Standard Stock solution: 100 mg of Tramadol was dissolved in 100 ml of 0.1N HCL (1000µg/ml)

Calibration curve of Tramadol in 0.1N HCL

From the above stock solution, 1 ml was transferred into a 10 ml volumetric flask and volume was adjusted to 10 ml that corresponded to 100 µg/ml Tramadol in solution. From that solution different aliquots of 0.2, 0.4, 0.6, 0.8, 1, 1.2 and 1.4 ml were transferred to 10ml volumetric flask, volume was adjusted with 0.1N HCL, which gave a concentration of 2,4,6,8 , 10,12 and14µg/ml of final standard. It was then observed for absorbance under UV double beam spectrophotometer at 272nm. The absorbance values are shown in table no: 2.

Table No: 2 Absorbance Values Of Tramadol.

S.no	Concentration (µg/ml)	Absorbance
1.	0	0
2.	2	0.09
3.	4	0.181
4.	6	0.229
5.	8	0.3
6.	10	0.36
7.	12	0.421
8.	14	0.494
Slope		**0.034054**
Intercept		**0.021**
R^2		**0.994**

In vitro dissolution test

It is the amount of the solid substance that goes into the solution per unit time under standard conditions of the temperature and pressure. Dissolution media was taken as 0.1N HCL, 900ml was placed in the vessel and the USP apparatus –I (Basket Method) was assembled. The medium was allowed to equilibrate to temp of 37 + 0.5°C. Tablet was placed in the basket and placed in the vessel; the apparatus was operated for 1 hour at 50 rpm. At definite time intervals, 5 ml of the fluid was withdrawn; filtered and again 5ml of the fluid was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed using UV. The results are shown in table no: **3**.

STABILITY STUDIES

FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human life. The ICH tripartite guidelines have established long term stability testing to be done at 250C/60%RH for 12 months. Accelerated stability testing should be done at 400 C/75%RH for 6 months and stability testing at intermediate storage conditions should be done at 300C/65%RH.

RESULTS AND DISCUSSION

Preformulation studies

All the prepared formulations were evaluated for bulk density, tapped density, % compressibility, hausner's ratio and angle of repose. The results of % compressibility, hausner's ratio and angle of repose were found to be between 10- 15, <1.25 and below 30 respectively. These results show that the formulations have very good flow properties. Table no: 3 shows the preformulation parameters of the powder blend.

Table No: 3 Preformulation Test Results.

Formulation	Bulk density gm/ml	Tapped density gm/ml	Carr's index%	Hausnerratio	Angle of repose
F1	0.25	0.29	12.5	1.14	25
F2	0.40	0.48	15.8	1.19	22
F3	0.33	0.40	16.67	1.20	21
F4	0.47	0.56	17.44	1.21	22
F5	0.30	0.38	20.58	1.26	26
F6	0.43	0.52	17.67	1.21	29
F7	0.36	0.43	16.79	1.20	22
F8	0.25	0.29	12.50	1.14	28

Preparation of calibration curve

A standard curve was plotted by taking absorbance of secondary stock solutions as obtained in table no: 2 and the graph obtained is shown in figure no: 1.

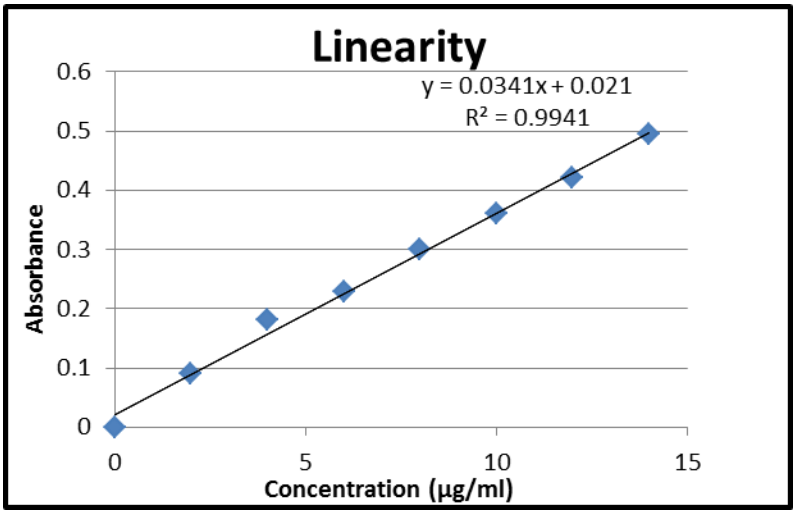

Figure No: 1 Calibration Curve Of Tramadol.

FT-IR data analysis for drug excipients compatibility studies

FT-IR spectra of the pure drug and the optimized formulation reveal no interaction between the drug and the polymers used. The spectra of pure and optimized formulation of Tramadol are shown in figure no: 2 and 3 respectively.

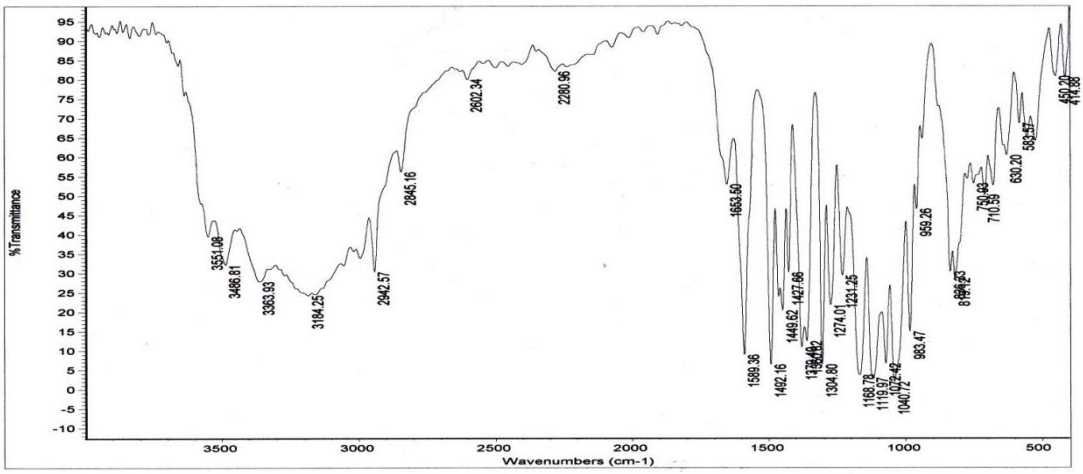

Figure No: 2 Ft-Ir Spectra Of Pure Tramadol Drug.

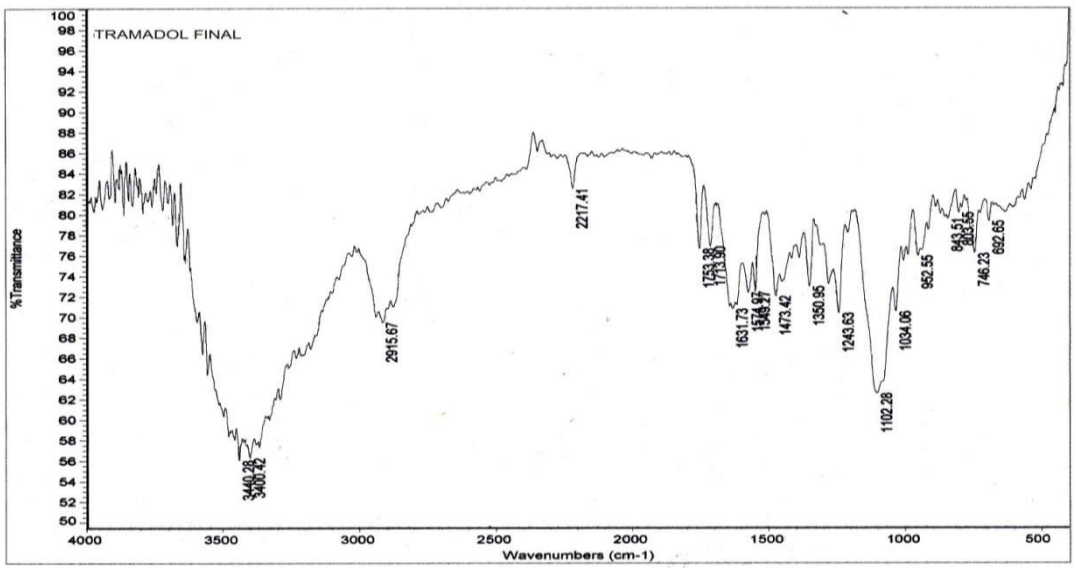

Figure No: 3 Ft-Ir Spectra Of Optimised Tramadol Drug Formulation.

Evaluation of tablet formulations

The prepared tablets were subjected to preliminary characterization such as hardness, thickness, % weight variation, friability and drug content determination. All the parameters were found to be within the acceptable range for all the formulations. The results of the evaluated formulations are shown in table no: 4.

Table No: 4 Post Formulation Test Results.

Formulation code	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Average Weight variation (mg)	Drug Content (%)	Disintegration Time (min)
F1	3.14	4.28	0.28	201	98.5	1min 25 sec
F2	3.44	4.01	0.26	200	98.7	1 min
F3	3.18	4.32	0.29	201	98.3	1 min 45 sec
F4	3.16	4.30	0.30	203	97.6	45 sec
F5	3.24	4.18	0.29	204	99.5	30 secs
F6	3.18	4.32	0.24	200	98.4	28 secs
F7	3.17	4.30	0.26	206	99.7	31 secs
F8	3.16	4.28	0.27	198	99.6	30 secs

In vitro dissolution studies

Table no: 5 shows the in vitro dissolution data of the formulations F1 to F8 and a graph is plotted taking cumulative % drug release on Y axis and time on X axis. The graph is shown in figure no: 4. From the results, it is observed that the dissolution profiles of the formulated products didn't meet the proper dissolution profile of Tramadol in 60mins. The formulations F6 and F8 showed 100% of drug release within 30mins. Between two formulations F6 is optimized because of lower concentration of subliming agent is preferred.

Table No: 5 In Vitro Dissolution Results.

Time	F1	F2	F3	F4	F5	F6	F7	F8
5 mins	7.81	15.61	8.91	10.14	15.8	26.68	16.24	29.21
10 mins	15.61	29.24	15.68	20.16	25.21	50.16	26.68	51.14
15 mins	21.18	40.80	20.21	39.24	40.86	70.24	39.68	71.89
20 mins	28.81	50.41	23.18	69.18	70.25	89.24	71.85	88.65
30 mins	33.81	61.86	27.38	78.21	85.64	100.18	84.42	100.24
60 mins	45.6	70.18	30.16	90.18	100.16	-	99.85	-

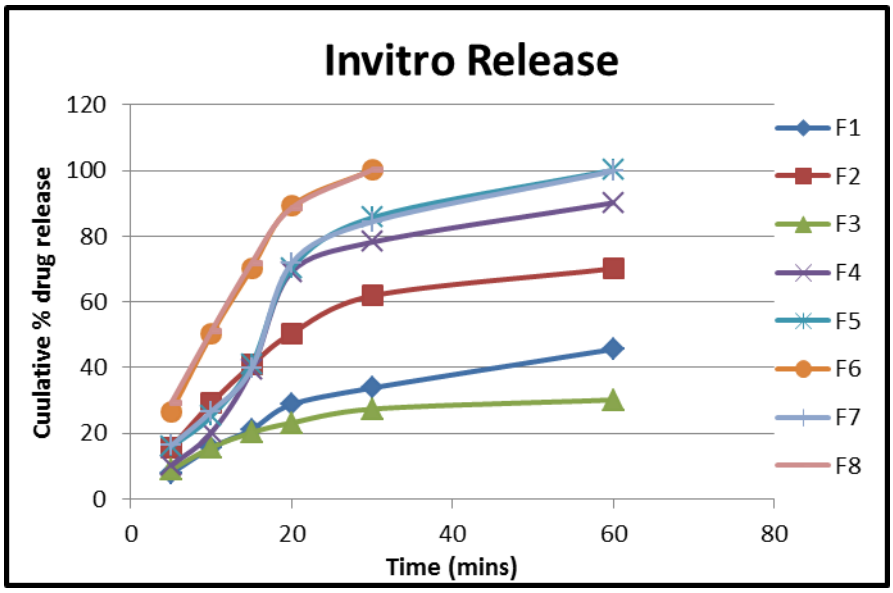

Figure No: 4 Graphical Representation Of In Vitro Drug Release.

Stability studies

Tramadol tablets of F6 formulation were packed in HDPE (High density polyethylene) container with child resistant caps (CRC) and induction sealed. These bottles were charged for stability study at 40^0C &75% RH. The physical evaluation was performed on the tablets after one month and three months and the results are shown in table no: 6. From the results, it was found that there was no effect on the tablets and was found to be within the limits according to ICH guidelines.

Table No: 6 Results Of Stability Studies Of F6 Formulation.

Parameter	Initial	400C / 75%RH	
		After one month	After three months
Colour	White	White	White
Surface	Smooth	Smooth	Smooth
Disintegration	28sec	25sec	35sec
Assay	98.40	98.40	97.70

CONCLUSION

Porous tablets of Tramadol were formulated using microcrystalline cellulose as filler, menthol as subliming agents, cross povidone and CCS and sodium starch glycolate as super disintegrant and magnesium stearate as lubricant. The evaluation of the tablets for various parameters, including in vitro drug release studies was also performed. The formulation F6 containing 5% of menthol showed disintegration time of less than 1min after drying. Menthol as subliming agent was found to be most effective of all other subliming agents as it had showed drastic effect on the drug release. All other parameters such as Hardness, Thickness, Weight variation and drug content were also found to be within limits. The disintegration time and drug content of the tablets were found to be satisfactory even after subjecting the tablets to stability studies at 40oC and 75%RH for 1 month and 3 months respectively. The formulation F6 and process can be easily scaled up and can be easily employed in large scale production because the process is simple, cost effective and precise and also yields reproducible good result that involves complex process for manufacturing the tablets.

Conflict of Interest:

Conflict of Interest declared none.

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