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DEVELOPMENT OF SUSTAINED RELEASE TRAMADOLOL HYDROCHLORIDE BY PELLETIZATION

*HARISH GOPINATH, G SYAM PRASAD, CH ANJANEYULU, SYED PEER BASHA
Department of Pharmaceutics, Nimra College of Pharmacy, Vijayawada-521 456,
***Corresponding author**: E Mail: harishgopinath4u@gmail.com

ABSTRACT

Tramadol Hydrochloride is a centrally acting analgesic. Tramadol acts as a μ-opioid receptor agonist, serotonin-nor epinephrine reuptake inhibitor (SNRI), NMDA receptor antagonist, 5-HT_2C receptor antagonist, nicotinic acetylcholine receptor antagonist and M_1 and M_3 muscarinic acetylcholine receptor antagonist. The aim of the present research is to develop and evaluate a better sustained release multiple unit pellets (MUP) formulation of Tramadol hydrochloride. Among the formulations the formulation F5 (5%w/w EC 50cps) was found to be as the best, which released the drug 94.2% at 24th hr and maintained its SR activity when compared with innovator. All the critical parameters like angle of repose, bulk density, tapped density and percentage drug content of F5 were good when compared with other formulations. The 94% drug release ensures the equivalence of formulation F5 (5%w/w EC 50cps) compared with innovator. From the above results, it can be concluded that F5 formulation showed the desired results and was found to be suitable for large scale production. The release mechanism was explored and explained with Higuchi and Hixon-croxwell equations, which indicates that pellets followed diffusion and erosion mechanisms for drug release. Accordingly, it can be concluded that the F5 (5%w/w EC 50cps) is robust one and the performance is less likely to be affected by the various factors studied. The formulations were kept at stability studies according to ICH guidelines for 3 months, which showed that all the formulations were stable.

KEY WORDS: Tramadolol HCl, Pellelts, Sustained, Pelletization.

1. INTRODUCTION

Pelletinization is an agglomeration process that converts fine powders or granules of bulk drug and excipients in small to free flowing spherical or semispherical units referred to as pellets. These usually range in size from 0.5-1.5mm (Raghavendra and Gandhi,2009). Pellets as a drug delivery system offer not only therapeutic advantages such as less irritation of the gastro-intestinal tract and a lowered risk of side effects due to dose dumping but also technological advantages like better flow property, less friable dosage for narrow particle size distribution, ease of coating and uniform packing. The reproducibility of the drug blood levels is an additional advantage to the use of a pellet formulation. Pellets disperse freely in the stomach of GIT so the invariably maximize drug absorption, reduce peak plasma fluctuation, and minimize potential side effects without appreciably lowering drug bioavailability. Pellets also reduce variation in gastric emptying rate and overall transit time (Indrajeet and Avinash,1997;Saleem and Ali,2008). Drug cause stomach upset can be given in the form of pellets, due to large surface area fastest absorption is possible. Pellets reduced peak plasma fluctuation thus, intra and inter-subject variability of plasma profile, which are common with single unit regimens, are minimized. Another advantage of pellets over single unit dosage forms is that high local concentration of bioactive agents. When formulated as modified-release dosage forms, pellets are less susceptible to dose dumping then the reservoir-type, single unit formulations (Atashkoyi,2008). The goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period of time. This is generally accomplished by attempting "zero-order" release from the dosage form. Zero-order release constitutes drug release from the dosage form which is independent of the amount of drug in the delivery system (i.e. a constant release rate). Sustained-release systems generally do not attain this type of release and usually try to mimic zero-order release by providing drug in a slow first-order fashion (i.e., concentration release dependent). Systems that are designated as prolonged release can also be considered as attempts at achieving sustained-release delivery(Traynor and Brown,2008). The term controlled- release drug product has been used to describe various types of oral extended release rate dosage forms, including sustained release (sustained action), prolonged release (long action) and retarded release. Pellets can be defined as small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5mm to 1.5mm, which are usually intended for oral administration, manufactured by the agglomerates of fine powders or granules of bulk drugs and Excipients using

appropriate processing equipment (Najib and Robert,2004). Pellets can be prepared by many methods, the compaction and drug-layering being the most widely used today. Regardless of which manufacturing process is used, pellets have to meet the following requirements. They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating. The particle size range should be as narrow as possible. The optimum size of pellets for pharmaceutical use is considered to be between 600 to 1000µm. The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits. A modified- release dosage form is defined "as one for which the drug release characteristics of time course and location are chosen to accomplish therapeutic convenience. Hence in the present research is to develop and evaluate a better sustained release multiple unit pellets (MUP) formulation of Tramadol hydrochloride (Zahid and Ghazala,2004).

2. MATERIALS AND METHODS

2.1 Materials: Tramadol Hcl was obtained as a gift sample from Lee Pharma, Starch has been obtained from Asaki Kayesi, PVP K-90, Sugar spheres, Talc, Ethyl Cellulose, Methylene dichloride, IPA.

2.2 Preparation of Tramadol Hydrochloride Sustained Release Pellets: Weigh the raw materials according to the manufacturing work order into double lined poly bags and affix dispensing labels with all details. Pulverize the Tramadol HCL powder thoroughly and collect in double lined polybag. Sieve through #30 mesh by using sifter. Load the sifted material along with the starch in double cone blender and mix for 30 minutes. PVP K90 is dissolved in isopropyl alcohol under stirring. Load the non-pariel seeds into coating pan and wet it by spraying the Solution from the above step and dust the blend powder till material stick to wet pellets, to form round spheres and repeat the operation till blend powder completes. Unload the drug pellets from the coating pan and load into tray drier for drying. Initially dry the pellets under the current of air for 30min switch on the heaters and maintain temperature from 28ºC-32ºC. Dry the pellets till the moisture content of pellets reduce to 1.5%w/v. Shift the pellets through sieve #18 mesh, followed by pass it through #25 mesh and label it as 18/25 fraction pellets. Take isopropyl alcohol and methylene dichloride in a stainless steel container, to this add Acetone under stirring continuously. To the above solution add ethyl cellulose by stirring and filter the solution through nylon mesh to get a uniform solution. Load the drug pellets into fluidized bed coater and spray the SR coating. Solution by using Fluidized bed coater Maintain the required conditions in coater(Raber and Schulz,1999;Moore and Crout,1998;Nobilis and Pastera,1996).

2.3 Drying and sifting for SR coated pellets: Initially dry the pellets under the current of air for 30min by using heaters and maintain temperature from 28ºC-32ºC. Dry the pellets till the moisture content of pellets reduce to 1.5%. Sift the SR coated pellets through sieve #12 mesh and collect the passing,followed by pass it through #16 mesh retained pellets and labeled as 12/16 fraction pellets.Totally 6 Formulation trails were done using the same procedure. During all the stages of the manufacturing process, temperature and humidity was maintained at 25 ± 5^0C and 50 ± 10 % RH. To optimize the formulation, the capsules were assay by U.V Spectroscopic method and drug release study. The formula of Trial 5 was optimized and selected for evaluation studies.The optimized batch 5 has been taken for further stability studies(Schulz and Raber,1992).

Table 1 In-process Parameters for Drug Coating

S.No	Process Parameters	Range
1	Inlet temperature	38-42ºc
2	Rpm of coating pan	10-15
3	spray rate (mg/min)	9-15
4	Atomization air	1-3

Table 2 In-process parameters for SR coating

S.No	Process parameters	Range
1.	Inlet temperature	38-42^{0}C
2.	Product temperature	32-36^{0}C
3.	CFC	800-2500
4.	Atomization	1-3
5.	Spray pressure(Barr)	3-4
6.	Peristaltic pump speed	12-18rpm
7.	Spray rate(mg/min)	8-12
8	Wruster height(mm)	20-60

Table 3 Formulations Table of Tramadol Hcl SR Pellets

	Ingredients (mg)	F1	F2	F3	F4	F5	F6
Drug coating	Tramadol HCl	50	50	50	50	50	50
	PVP K-90	4.4	4.4	4.4	4.4	4.4	4.4
	Sugar pellets	22.5	22.5	22.5	22.5	22.5	22.5
	Lactose	30	30	30	30	30	30
	IPA (ml)	56	56	56	56	56	56
SR coating	EC 7cps	1.058	1.6	2.3	---	---	---
	EC 50cps	---	---	---	2.7	5.1	7.5
	PEG2000	0.07	0.07	0.07	0.23	0.23	0.23
	IPA (ml)	14	14	14	44	44	44
	Acetone (ml)	6	6	6	30	30	30
	MDC (ml)	15	15	15	36	36	36

3. RESULTS AND DISCUSSION

Tramadol Hcl is a centrally acting analgesic which gives relief from severe cancer pain. The main aim of the present work was to formulate and evaluate the Tramadol Hcl SR pellets prepared by Wurster process. When pre-formulation studies were carried out, the colour of the drug loaded pellets was found almost white and round shape. FTIR analysis between the drug and SR polymer mixture showed no unaccountable extra peaks, which confirms the absence of chemical interactions showed in figure.2. Pellets prepared by solution or suspension coating process containing some moisture content, which was determined with loss on drying of 2.5%w/w. To fill the pellets into capsule shell angle of repose, tapped density, bulk density and Carr's index were very important, because they influenced flow property of pellets and the values were found to be as 28.1^0, 0.84gm/ml, 0.72gm/ml and 14.28% was shown in table.6.. Hence the results states that Tramadol Hcl pellets had good flow property to fill into the capsule shell. The release rate of the drug was depends on the particle size, the average particle size was determined as 1.306mm.UV-Visible double beam spectrophotometer was used to determine the percentage drug content at 271nm.All the formulations showed percentage of drug content of around 100±5% shown in table.7. The surface of pellets was found to be as smooth by viewing through SEM analysis shown in figure.1.

Dissolution studies were carried out up to 24hrs to study the drug release mechanism. The results of the formulations at the end of 24hr was 89.4%,84.2%,86.1%,90.1%,94.2% & 80.3% respectively shown in table.8 and figure.3. The dissolution profile was given in figure.3, mean dissolution time of pellets were given in Table No.8. The formulations F1, F2, F3 were prepared by using EC 7cps as SR polymer. But the drug release was not a SR, because EC 7cps did not have the capability to show SR effect. So in the formulations F4, F5 and F6, the grade of EC 7cps changed to EC 50cps with different concentrations. The formulations F4 (2.5%w/w EC 50cps) and F5 (5%w/w EC 50cps) showed the SR effect. But F5 formulation had the drug release same as innovator. Further increased in concentration of EC 50cps i.e. 7.5%w/w (F6) showed no drug release for a long period, due to more concentration of SR coating polymer. The r^2 value of the formulated batch F5 was 0.97 shown in table.7. The drug release mechanism of F5 followed the Higuchi release kinetics and Hixon-crowl, which suggested that the drug release mechanism followed both diffusion followed erosion mechanisms.

S.No	Characteristics	Results
1	Physical appearance	A white (or) almost white powder, odorless.
2	Solubility	Sparingly soluble in water and soluble in Methanol, practically soluble in Methylene chloride.
3	Bulk density	0.72gm/ml
4	Tapped density	0.84gm/ml
5	Compressibility index	14.28%
6	Melting point	180-184^{0}C
7	Molecular weight	299.84.

Table 4 Pre-formulation Study of Active Pharmaceutical Ingredient

Table 5 Drug Excipient Compatibility Studies

Composition Details	Observations (Storage condition/ Duration					
	Initial	$40^{O}C/75\%RH$			$60^{O}C$		$2\text{-}8^{O}C$
		1M	2M	3M	15D	30D	3M
Tramadol HCl	A White colour powder	NCC	NCC	NCC	NCC	NCC	NCC
Tramadol HCl and Sugar spheres (30-35mesh)	A White colour powder	NCC	NCC	NCC	NCC	NCC	NCC
Tramadol HCl and Plasidone S-630	A White colour powder	NCC	NCC	NCC	NCC	NCC	NCC
Tramadol HCl and Lactose	A White colour powder	NCC	NCC	NCC	NCC	NCC	NCC
Tramadol HCl and ethyl cellulose	A White colour powder	NCC	NCC	NCC	NCC	NCC	NCC
Tramadol HCl and PEG 2000	A White colour powder	NCC	NCC	NCC	NCC	NCC	NCC

NCC-No Color Change

Table 6 Pre-formulation Characteristics

Formulations	F1	F2	F3	F4	F5	F6
Angle of Repose (º)	28.7	26.4	27.3	25.9	28.1	26.5
Bulk Density(gm/ml)	0.72	0.78	0.74	0.71	0.72	0.73
Tapped Density (gm/ml)	0.86	0.89	0.86	0.87	0.84	0.85
Compressibility Index (%)	16.27	12.35	13.95	18.39	14.28	14.11
Moisture Content (%)	2.41	2.42	1.92	2.63	2.34	2.45

Table.7 Chemical Evaluations of Drug Content

	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Assay (%)	104	99.25	104.75	102	101.4	98.5

Table.8 *In-vitro* Dissolution Studies

S.No	Dissolution Time(hr)	**Percentage Drug Release (%)**						
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**Innovator**
1	1	28.4	23.4	21.9	18.3	18.1	11.4	18.6
2	2	40.8	36.9	33.8	22.6	31.7	19.6	31.5
3	4	47.2	44.6	38.6	28.4	48.0	56.9	39.8
4	8	61.3	64.9	48.4	54.9	61.5	69.4	60.7
5	12	73.8	76.5	60.4	80.3	83.2	71.4	83.1
6	24	89.4	84.2	86.1	90.1	94.2	80.3	96.1

Table.9 Correlation Coefficient of Drug Release

Formulation	**Zero Order**		**Higuchi**		**Kosemayer plot**		**First Order**		**Hixon Crowl**	
	R	**K**	**R**	**k**	**r**	**k**	**R**	**k**	**r**	**K**
F1	0.861	5.051	0.981	17.73	0.994	0.869	0.987	0.037	0.964	0.091
F2	0.862	5.622	0.972	17.83	0.983	0.903	0.953	0.032	0.928	0.083
F3	0.934	4.111	0.992	16.66	0.988	0.876	0.988	0.032	0.982	0.083
F4	0.927	6.136	0.976	20.05	0.974	0.986	0.979	0.043	0.966	0.106
F5	0.901	6.257	0.984	20.47	0.983	0.982	0.991	0.051	0.972	0.116
F6	0.815	6.149	0.936	18.40	0.927	1.049	0.895	0.029	0.868	0.079

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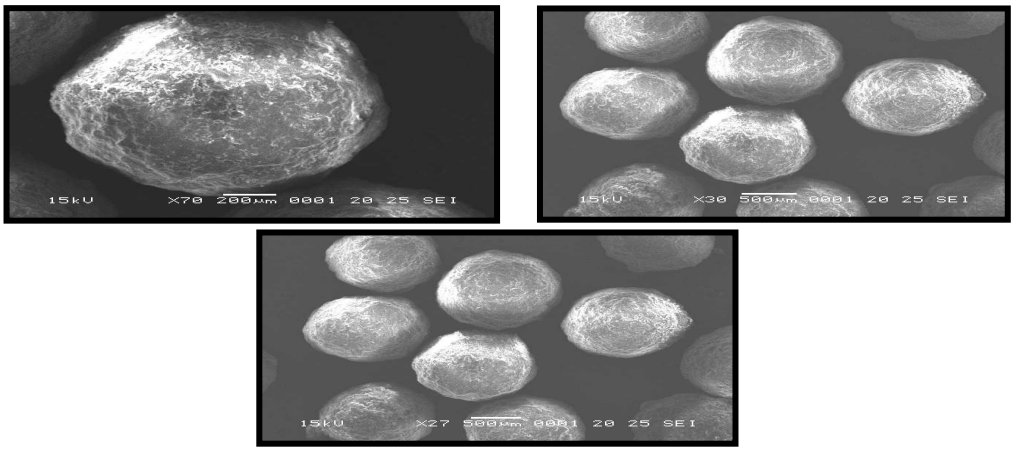

Figure.1 SEM Photograph of Formulation F5

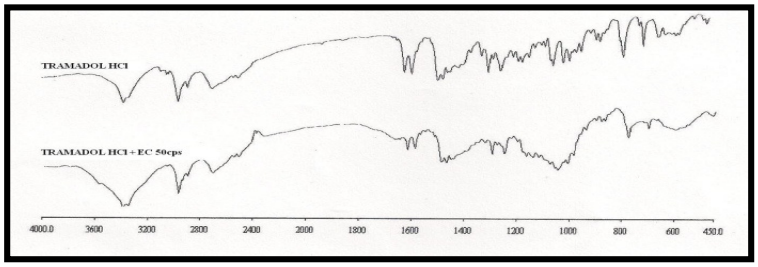

Figure.2 Drug Polymer Interaction Study (FTIR Studies)

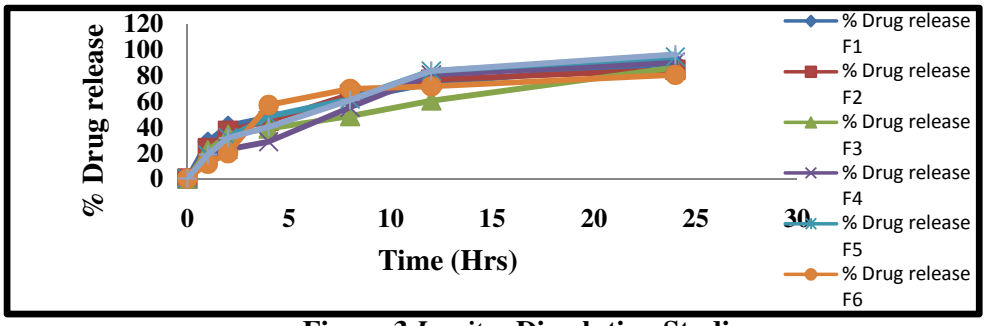

Figure.3 *In-vitro* Dissolution Studies

Table.10 Stability Studies of Tramadol Hcl at the end of first Month

Conditions	**Intial**	**25°C/60% RH**	**30°C/65% RH**	**40°C/75% RH**
Physical Appearance	White to off White Spherical Pellets	Colouris intial but shape is not uniform	Colour is intial but shape is not uniform	Colour is intial but shape is not uniform
Moisturecontent(%)	3.1	3.3	2.7	2.9
Drug content (%)	101.4	98.9	99.4	97.5
Dissolution				
1st hr	18.1	16.55	17.16	18.92
2nd hr	21.7	39.45	33.39	34.64
4th hr	48.0	48.56	47.45	42.45
8th hr	61.5	68.75	61.32	66.67
12th hr	83.2	87.31	86.45	85.43
24th hr	94.2	92.85	95.46	96.67

Table.11 Stability Studies of Tramadol Hcl at the end of second Month

Conditions	Initial	25°C/60% RH	30°C/65% RH	40°C/75% RH
Physical Appearance	White to off White Spherical Pellets	Colour is intial but shape is not uniform	Colour is intial but shape is not uniform	Colour is intial but shape is not uniform
Moisturecontent(%)	3.3	3.2	2.8	2.4
Drug content (%)	100.12	97.6	98.7	99.4
Dissolution				
1st hr	19.3	17.8	18.3	17.6
2nd hr	24.2	30.4	31.6	30.8
4th hr	45.7	47.6	48.4	45.9
8th hr	60.84	60.4	63.8	62.3
12th hr	87.98	82.6	84.1	82.8
24th hr	95.23	93.8	92.4	93.6

Table.12 Stability Studies of Tramadol Hcl at the end of third Month

Conditions	Intial	25°C/60% RH	30°C/65% RH	40°C/75% RH
Physical Appearance	White to off White Spherical Pellets	Colour is intial but shape is not uniform	Colour is intial but shape is not uniform	Colour is intial but shape is not uniform
Moisturecontent(%)	3.3	3.1	2.6	2.8
Drug content (%)	102.4	99.8	97.6	98.4
Dissolution				
1st hr	19.6	17.4	16.25	19.58
2nd hr	22.78	42.56	34.21	36.78
4th hr	49.45	44.85	47.42	45.78
8th hr	62.58	67.58	63.47	66.25
12th hr	83.25	37.24	78.96	87.35
24th hr	93.25	94.71	96.42	97.41

4. CONCLUSION

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain acts as a warning signal against disturbances either in the body or in the external environment of an individual. Pain arising from the skin and from the deep structure like muscles, bone and joints is also termed as somatic pain. This is generally caused by inflammatory reaction in the tissues. Tramadol acts as a μ-opioid receptor agonist, serotonin-nor epinephrine reuptake inhibitor (SNRI), NMDA receptor antagonist, 5-HT_{2C} receptor antagonist, $(\alpha 7)_5$ nicotinic acetylcholine receptor antagonist and M_1 and M_3 muscarinic acetylcholine receptor antagonist. The analgesic action of Tramadol has yet to be fully understood, but it is believed to work through modulation of serotonin and nor epinephrine in addition to its mild agonism of the μ-opioid receptor. The present work was to develop SR Tramadol pellets by Wurster process. Among the formulations the formulation F5 (5%w/w EC 50cps) was found to be as the best, which released the drug 94.2% at 24th hr and maintained its SR activity when compared with innovator. All the critical parameters like angle of repose, bulk density, tapped density and percentage drug content of F5 were good when compared with other formulations. The percentage cumulative amount of drug release for formulated batch F5 was found to be around 95% w/v compared to that of the innovator sample which ensures the equivalence of F5 (5%w/w EC 50cps) with innovator (Table no.7). From the above results, it can be concluded that F5 formulation showed the desired results and was found to be suitable for large scale production.

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