International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.6, No.5, pp 1736-1745, Sept-Oct 2014

Formulation and Evaluation of Sustained Release Pellets of Tramadol HCl Using 3^2 Full Factorial Design

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Abstract: The present research concerns the formulation and evaluation of sustained release pellets filled capsule of opioid analgesic, Tramadol HCl. Development of sustained release dosage form is to maintain therapeutic blood levels of the drug for extended period of time. Sustained release formulation provides uniform concentration at absorption site, maintains plasma concentration within a therapeutic range, reduces the dosage frequency and minimizes the side effects (nausea) associated with drug by avoiding dose dumping effect. Oral sustained release pellet formulations of Tramadol HCl were prepared using extrusion-spheronization technique. Pellets provide specific advantages of smoother plasma concentration profile and gradual absorption than tablet. HPMC K100M and EC along with the coating of Eudragit RSPO were chosen to achieve the desired dissolution profile. Their concentrations were optimized using 3^2 full factorial design to achieve the aim of sustaining the drug release for 12 hours. The prepared pellets were studied for different flow properties and drug release studies.
Keywords: Tramadol HCl, Sustained release pellets, extrusion-spheronization, HPMC K100M, EC

Introduction:

Development of sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for extended period of time. Sustained release drug delivery systems provide a uniform concentration at absorption site, maintained plasma concentration within a therapeutic range, reduce the frequency of administration and minimizes the side effects[1]. The most commonly used method of modulating the drug release is a matrix system. Novel drug delivery systems has advantages such as ease of administration, sustained release of drug at continuous rate, effectiveness in the treatment of chronic conditions and better patient convenience due to simplified dosing schedule [1].

Pellets are small discrete units, each exhibiting desired characteristics. In these systems, the dosage of the drug substances is divided into subunits typically consisting of spherical particle [2]. Pelletization is a term used to define agglomeration of drug substances in either powder or granule form resulting in the form of semi spherical and spherical agglomerates having good flow properties [1] .The particle

-Spheronization Process:

Extrusion-spheronization technique is used to formulate sustained release formulation having smooth surface, narrow size distribution in order to achieve uniform coating and free flowing agglomerates. The main objective is to produce pellets of uniform size with high drug loading capacity

1. Pellets Preparation Method[3]:

Dispensing and sifting:

Wet massing: By using 3% starch paste.

Extrusion: Pass the wet mass through the extruder while keeping screen size constant.

Spheronization: Extrusion involves applying pressure to a wet mass until it passes through the opening of a screen plate of extruder and further shaped into small extrudate segments which eventually break down their own weight.

Drying: Dry the pellets in hot air oven for 15min at 40ºC

Coating: Prepare 15% w/v solution of coating material in ethyl acetate. Load the pellets in pan coater**.** Process parameters for coating are: Inlet air temperature - 30ºC to 40ºC and Air flow – 1 bar

Capsule Filling:

Tramadol HCl per capsule - 101.4 mg

Total fill weight per capsule - 321.4 mg

Thus capsule shell size '0' was used for filling the pellets.

Total Dose [4]:

Volume of distribution V_d = 2.6 L×50kg = 130 L

Cl (Clearance) $= (0.693 \times V_d)\, t_{1/2}$
$= (0.693 \times 130)/6.5$
$=13.86$ L/ hr

Css (steady state concentration) = $F \times D/Cl \times \tau$

Where, F= Fractional bioavailability
D=Dose (mg)
Cl=Clearance(L/hr)
τ =Dosing frequency (hr)

Css = (0.85×50)/(13.86×12)
= 0.2555 mg/L

L_D (Loading dose) $= (Css \times V_d)/F$ (mg×L/L)
$= (0.2555 \times 130)/0.85$
= 39.08 mg

M_D (maintenance dose) $= (Css \times Cl \times \tau)/F$
$= (0.2555 \times 13.86 \times 12)/0.85$ (mg/L)×(L/hr)×(hr)
= 49.99mg

Totale dose = $L_D + M_D$ = 39.08 + 49.99 = 89.07mg

Calculation for Salt of Tramadol [5]:

Molecular weight of Tramadol = 263.375 gm/mol

Molecular weight of Tramadol HCl= 299.84 gm/mol

Cf (correction factor) = Mol weight of base

Mol weight of salt form

= 263.375

299.84
= 0.8783

Quantity of salt = Quantity of base/Cf
= 89.07/0.8783
= 101.4mg

Evaluation Parameters:

Densities [12]: Loose bulk density (LBD) and tapped bulk density (TBD) for the blend was performed by using glass cylinder tapping method.

Friability Test [13]: The friability was found in all designed formulations in the range 0.35 to 0.65 % to be well within the approved range (<1%).

Assay: 100mg equivalent pellets were crushed and dissolved in 100ml of PBS pH6.8. Which if further diluted to 10ml and absorbance was measured in UV visible spectrophotometer at λ_{max} 268nm

Particle size Distribution [14,15]: 100gm of pellets were weighed using electronic weighing balance. Pellets were transferred to set of sieves having different mesh size for particle size analysis. Calculate the % .

retained on the each sieve which was tabulated

Response Surface Analysis [17]: Response surface methodology (RSM) is a collection of mathematical and statistical techniques for empirical model building. By careful design of experiments, the objective is to optimize a response (output variable) which is influenced by several independent variables (input variables). Experimental design has several advantages over the classical one-step approach. It improves performance characteristics, reduced cost, shortened development and testing times. This method is used to assure the performance of the selected polymers.

Residual Solvent Test [19]: Residual solvent test of Ethyl acetate was done according to IP 2014

SEM Analysis: SEM analysis of coated pellets was done.

Kinetic model [4]: The value of F7 batch showed the highest R^2 value for Higuchi model. This indicates that the drug release is by the diffusion and erosion both mechanisms. The release exponent value N for Korsmaeyer -peppas is 0.6579(standard range 0.5 - 0.85) obtained indicates drug release by anomalous (non-fickian diffusion) diffusion.

Stability study [20]: For stability testing the samples of optimized pellets were kept at 40 ºC/75% RH for one month in petri plate. Then samples were withdrawn and analyzed for physical and chemical evaluation or whether any kind of change takes place in organoleptic characters and assay.

Result and Discussion

1.Full factorial design 3^{2} [16] :

Table 1.1 Independent variables and Levels

Indpendent Variables	Levels		
X1(HPMC K100M) Coded value	-1	0	+1
Actual value	10%	15%	20%
X2 (Ethyl cellulose) Coded value	-1	0	+1
Actual value	30%	35%	40%

Table 1.2 Tramadol HCl Formulation Factorial Design [6,7,8,9,10,11]

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tramadol HCl (mg)	101.4	101.4	101.4	101.4	101.4	101.4	101.4	101.4	101.4
HPMC K 100 M (%)	10	15	20	10	15	20	10	15	20
EC (%)	30	30	30	35	35	35	40	40	40
MCC (%)	30	30	30	30	30	30	30	30	30
Lactose (%)	25	20	15	20	15	15	15	10	5
PVP K30(%)	5	5	5	5	5	5	5	5	5
Coating(12% weight gain)									
Eudragit RSPO (%)	12	12	12	12	12	12	12	12	12
Ethyl acetate	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total weight per capsule(mg)	321.4	321.4	321.4	321.4	321.4	321.4	321.4	321.4	321.4

Evaluation of factorial design batches:

Table 1.3: Physical Evaluation

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angle of repose	22.80	23.45	24.18	21.34	20.94	23.55	20.67	20.01	23.43
Bulk density(gm/ml)	0.468	0.502	0.526	0.523	0.453	0.514	0.411	0.513	0.487
Tapped density(gm/ml)	0.511	0.521	0.555	0.541	0.499	0.527	0.434	0.535	0.515
%Friability	0.531	0.512	0.555	0.600	0.517	0.611	0.501	0.531	0.497
Particle Analysis(gm retained on each sieve)									
16#	4.53	5.12	6.22	5.42	5.87	5.96	6.46	4.78	4.91
20#	0.462	0.345	0.282	0.227	0.260	0.21	0.254	0.434	0.338
24#	0.057	0.012	0.020	0.033	0.027	0.018	0.012	0.088	0.052
44#	0.05	0.01	-	0.003	-	0.001	-	0.012	0.022
Assay %	98.8± 0.1	98.64± 0.0152	99.21 ±0.0 230	97.14±0 .01	100.12±0 .0152	99.39± 0.01	101.3 ±0.01 52	98.8± 0.01	101.1±0. 0115

Drug Release Profile:

Table 1.4: Factorial design drug release profile

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
%CDR									
0.5	30.17	23.07	19.52	17.75	23.07	30.17	7.1	10.65	9.34
1	41.05	39.18	40.93	33.9	49.83	60.52	14.04	33.78	23.07
1.5	51.87	48.27	55.36	57.09	66.08	62.63	30.29	39.29	30.34
2	64.58	64.51	59.22	62.73	83.42	66.52	39.55	50.16	41.16
3	83.66	87.7	82.95	81.14	95.06	78.5	61.96	73.24	58.91
4	91	95	91.24	84.52	98.24	83.63	69.85	80.17	68.55
5	94.94	98.86	93.19	85.42	98.55	84.64	74.45	81.25	72.91
6	97.72	-	95.66	85.76	-	84.88	77.81	84.08	76.19
7	-	-	97.41	91.61	-	87.29	79.72	84.97	78.39
8	-	-	-	97.51	-	92.8	81.93	87.83	83.69
9	-	-	-	-	-	99.32	83.91	92.51	91.08
10	-	-	-	-	-	-	87.3	98.53	93.96
11	-	-	-	-	-	-	92.21	-	94.27
12	-	-	-	-	-	-	98.93	-	99.57

(0.5 to 2 hour in dissolution media 0.1 N HCl and remaining hours in Phosphate buffer pH6.8)

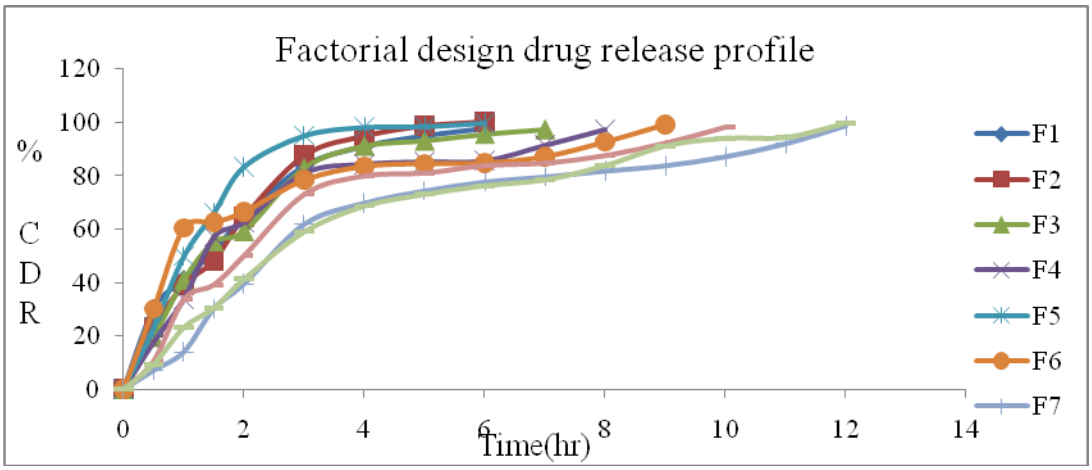

Figure 1.1: Factorial design drug release profile

Conclusion: From the result shown in figure it can be concluded that according to % cumulative drug release batch F7 and F9 show sustained release up to 12 hours. But for batch F7 the loading dose is nearer to the calculated loading doseand it requires less time of spheronization than F9. So F7 is an optimized batch.

2. Regression Analysis for effect of X1 and X2 on Y1 and Y2: [16,17]

Output of Regression Analysis for effect of X1 and X2 on Y1 (%CDR on 6th hour)

Full Model Polynomial equation

Y1=95.75-0.75X1 - 9.266X2 - 8.396X12 - 1.526X22 + 0.11X12

Reduced Model Polynomial equation

Y1=94.73-9.166X2 -8.396X12

The regression analysis of X_1 and X_2 on Y_1 was calculated and it shows that in reduced model equation factor X_2 and X_1^2 are having negative sign which shows the negative effect on the drug release.

Output of Regression Analysis for effect of X1 and X2 on Y2 (Pellets retained on 16#)

Full Model Polynomial equation

$Y_1=4.4711 - 0.1X_1 + 0.138X_2 + 1.033X_1^2 – 0.4316X_2^2 – 1.147X_{12}$

Reduced Model Polynomial equation

$Y_1=4.188 – 1.033X_1^2 -1.147X_{12}$

The regression analysis of X_1^2 and X_{12} on Y_1 were calculated and the reduced model equation shows that factor X_1^2 and X_{12} are having negative sign which shows the negative effect on the drug release.

3. Generation of Contour plots, response surface plot and Overlay plot for responses:

Generation of Contour plots and response surface plot for response Y1 (%CDR at 6th hour)

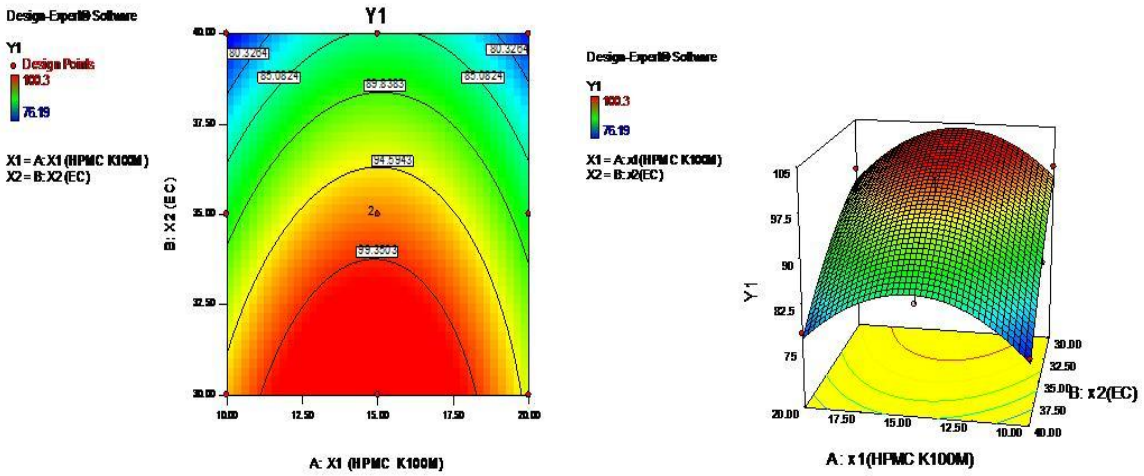

Figure 1.2: Contour Plot and Response Surface Plot for Response Y1

Conclusion: From this plot it can be concluded that X1 (Conc. of hypromellose) and X2 (Conc. Of ethyl cellulose) have negative effect on the drug release (%CDR) to have sustained released pellets. So, increase in concentration of Hypromellose and ethyl cellulose will decrease the drug release.

Generation of Contour plots and response surface plot for response Y2 (Pellets retained on 16#)

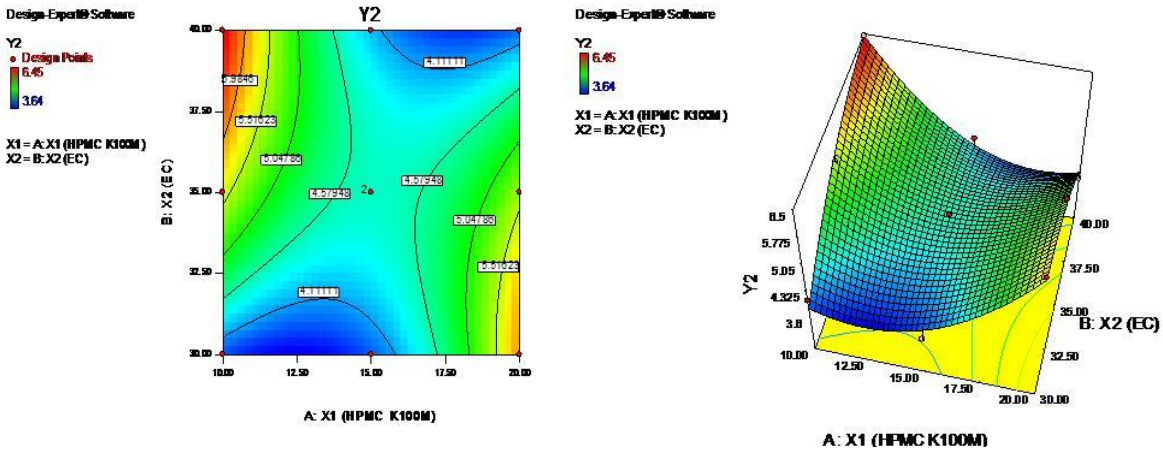

Figure 1.3: Contour Plot and Response Surface Plot for Response Y2

Conclusion: From this plot it can be concluded that X1 (Conc. of hypromellose) and X2 (Conc. Of ethyl cellulose) have negative effect on the size of pellets. So, increase in concentration of Hypromellose and ethyl cellulose will decrease the size of pellets

4. Overlay Plot for check point batches:

Three check point batch was prepared to find the efficiency of f ull model equations generated previously using 3^2 full factorial designs.

1.Check point batch using X1=11.35% of Hypromellose

X2=37.33% of Ethyl cellulose

2.Check point batch using X1=17.17% of Hypromellose

X2=33.26% of Ethyl cellulose

3.Check point batch using X1=12.73% of Hypromellose

X2=39.11% of Ethyl cellulose

Table 1.5: Comparison between the experimental and Practical values for the check point batches

Response		Check point batch		
		Predicted	**Experimental**	**%PE**
Y1(%CDR)	Check point batch 1	87.258	86.798	0.527
	Check point batch 2	96.166	96.289	-0.128
	Check point batch 3	85.80	85.23	0.664
Y2(pellets retained on 16# in gm)	Check point batch 1	5.472	5.389	1.5
	Check point batch 2	4.717	4.690	0.572
	Check point batch 3	4.951	4.879	1.4

Conclusion: The result of drug release at 12th hour shows that batch F7 has sustained the drug release for 12 hours and the loading dose is 40.1mg which is nearer to the calculated loading dose (39.08mg). Thus the certain evaluation parameters are evaluated for the F7 batch.

5. Evaluation parameters

5.1 Content Uniformity [18]:

Table: 1.6 Content Uniformity Test

Unit	Assay (%)		
1	99.43		
2	100.35	Mean	99.259
3	98.28	Standard Deviation	1.32219
4	97.64	M value	99.259
5	101.31	AV	3.1728
6	100.20		
7	97.16		
8	99.16		
9	98.73		
10	100.33		

Observation: For the drug the calculated AV value was 3.172 which is less than L1% (15).

Conclusion: Prepared formulation complies the content uniformity test for API

5.2 Residual Solvent Test [19]:

Ethyl acetate –Found in range of 34.57ppm (limit is 5000ppm)

5.3 SEM Analysis:

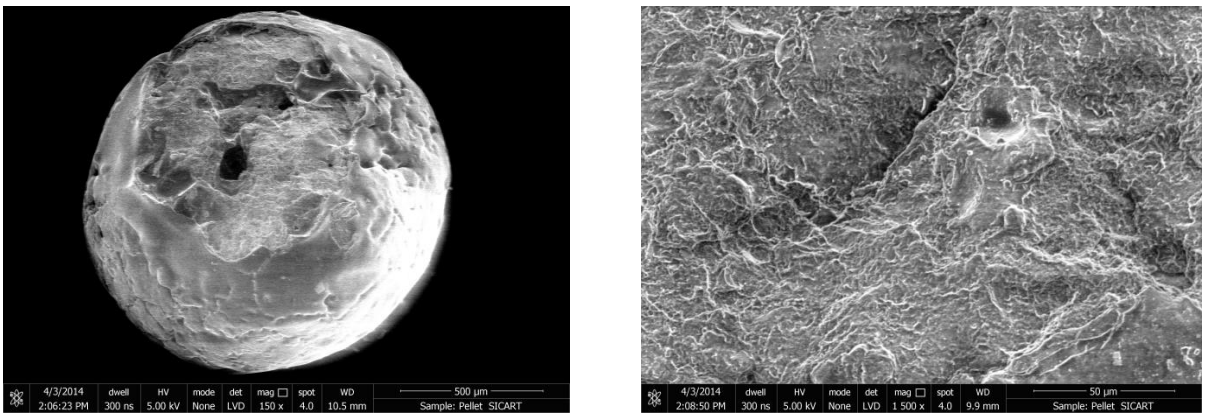

Figure 1.4: SEM Photographs of Pellets

5.4 Kinetic model [4]:

Table 1.7: Release kinetic of optimized Batch (F7)

Kinetic Model	Regression(R^2)	N value for Korsmeyer-Peppas
	F7	F7
Higuchi	0.9683	0.6579
Zero Order	0.8987	
First Order	0.6987	
Hixson-Crowell	0.8061	
Korsmeyer-Peppas	0.9372	

5.5 Stability study [20]:

Table 1.8: Organoleptic characteristic and Assay of optimized batch (F7)

Parameters	Initial	40°C/ 75% RH	
		Before 1 Month	After 1 Month
Color	White	White	Light Yellow
Odor	Odorless	Odorless	Odorless
Assay	99.15 ± 0.38	99.10 ± 0.42	98.7 ± 1.04

*: Optimized pellets are kept in stability chamber for further 1 month study.

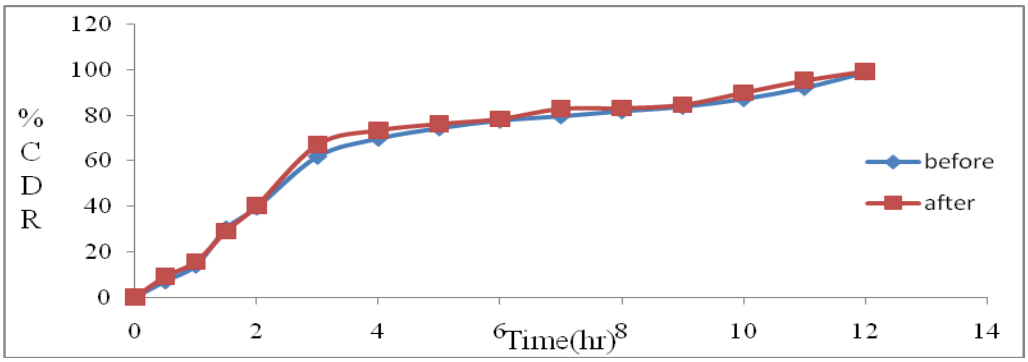

Figure 1.5: Stability study (% CDR of before and after 1 month)

Table 1.10: Comparison of stability study data of before 1 month and after 1 month

t-Test: Paired Two Sample for Means		
Observation	Before 1 month %CDR	After 1 month %CDR
Mean	64.21786	65.93857
Variance	871.479	888.126
Observations	14	14
Pearson Correlation	0.998595	65.93857
Hypothesized Mean Difference	0	
Df	13	
t Stat	-4.03084	
P(T<=t) one-tail	0.000713	
t Critical one-tail	1.770933	
P(T<=t) two-tail	0.001427	
t Critical two-tail	2.160369	

Conclusion:

Apply the t-test for both Before 1 month and after 1 month %CDR of formulation F7. The result in table 1.34 shows that the is no significance difference in %CDR of two formulations. The tabulated value is higher than the calculated value for both one and two tailed tests. This concludes that there is no significant difference between two formulations and the formulation after 1 month is stable.

Result:

A novel drug delivery system can be prepared to produce analgesic effect in post surgical pain, chronic pain and acute musculosketetal pain and as an adjuvant to NSAID therapy in patients with osteoarthritis. The sustained release pellets of Tramadol HCl was prepared by extrusion-shperonization technique. 3^2 full factorial design was applied by using different concentrations of HPMC K 100 M (X1) and Ethyl cellulose (X2) as independent parameters. Coating of Eudragit RSPO (12% and 15% weight gain) was applied to all the batches. The dissolution profile and particle size of the pellets were taken as the dependent factors for factorial design. The optimized pellets formulation (Batch F7) have sustained the drug release up to 12 hours and had produced pellets size in range. Check point batches were taken to assure the performance of the optimized formula. The optimized formulation (Batch F7) and marketed formulation (Contramal SR tablet) of Tramadol HCl was compared. This showed the formulated batch had better sustained release action than marketed. Stability study of capsule showed that there was no major effect of temperature and humidity on assay and *In vitro* dissolution. So, pellets filled capsule of Tramadol HCl is stable formulation.

Thus, an attempt was made to design the rugged, effective and stable formulation which was feasible, advantageous and patient compliant.

Experience with pellet filled capsule reveals that this is a fruitful approach to prepare Pellets filled capsule for better action of Tramadol HCl.

Conclusion:

The combination of HPMC K100M (10%), EC (40%) and coating of Eudragit RSPO (12% and 15% weight gain) was used to formulate the pellets. This formulation successfully achieves the aim of sustaining the release of drug up to 12 hours.

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