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Formulation and Evaluation of Sustained Release Pellets of Tramadol HCl Using Different Release Retarding Polymers

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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. Various polymers like Hydroxy propyl methyl cellulose (HPMC K100M), Carbopol 974 P, Xanthan gum, Ethyl cellulose and Eudragit RSPO were used to screen the best polymer combination through preliminary formulations. HPMC K100M, EC and coating of Eudragit RSPO were screened 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. A wide range of polymers has been employed as release retarding agents. 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 sizes of the resulting pellets are between 0.05mm and 2mm [2]. Extrusion-spheronization is the most commonly used method for pellet production[1].

Materials and Methods:

Tramadol HCl was gift sample from Shital Chemicals, Naroda, Methocel K100M, (Colorcon Asia Pvt ltd, Goa, India), Eudragit RSPO (Evonik, India), EC Ethyl cellulose (Taian Ruitai Cellulose Co. Ltd (China) and all other ingredients were obtained from ACS Chemicals. All ingredients were of analytical reagent grade.

Experimental Work:

1. Pellets Preparation Method [3]:

Dispensing and sifting: Weigh all the ingredients and sift through 40# separately.

Wet massing: Mix drug, diluents and polymers properly.Prepare 3% starch paste.

Add starch paste drop wise in to the powder blend and mix it properly and prepare dough mass.

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:

- Inlet air temperature - 30ºC to 40ºC
- 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 × 130)/6.5

=13.86 L/ hr

Css (steady state concentration)= F×D/Cl × τ

Where, F= Fractional bioavailability

D= Dose (mg)

Cl= Clearance(L/hr)

τ = Dosing frequency (hr)

Css = (0.85 x50)/(13.86x12)

= 0.2555 mg/L

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

= (0.2555×130)/0.85

= 39.08 mg

M_D (maintenance dose) = (Css×Cl× τ)/F

= (0.2555×13.86×12)/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 the 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 in Table 1.2.

Result and Discussion:

1. Formulations to optimize single polymer [6-11]:

Polymers used in preliminary formulations were: Carbopol, Xanthan gum, HPMC K100M, Eudragit RSPO.

Table 1.1: Formulation containing: Carbopol, Xanthan gum, HPMC K100M, Eudragit RSPO

Ingredients	**C1**	**C2**	**C3**	**X4**	**X5**	**X6**	**H7**	**H8**	**H9**
Drug Tramadol HCl (mg)	101.4	101.4	101.4	101.4	101.4	101.4	101.4	101.4	101.4
Carbopol 974P (%)	0.5	1	2	-	-	-	-	-	-
HPMC k 100 M (%)	-	-	-	-	-	-	8	12	16
Xanthan gum (%)	-	-	-	10	20	30	-	-	-
EC (%)	-	-	-	-	-	-	-	-	-
MCC (%)	59.5	59	58	50	45	40	55	53	52
Lactose (%)	35	35	35	35	35	25	35	30	28
PVP K30 (%)	5	5	5	5	5	5	5	5	5

Ingredients	**E10**	**E11**	**R12**	**R13**
Drug Tramadol HCl (mg)	101.4	101.4	101.4	101.4
EC (%)	20	40	-	-
Eudragit RSPO (%)	-	-	8	12
MCC (%)	59.5	59	58	50
Lactose (%)	35	35	35	35
PVP K30 (%)	5	5	5	5

Table 1.2: Evaluations of Formulation containing: Carbopol 974P, Xanthan gum, HPMC K100M, Eudragit RSPO [15]

Parameters	**C1**	**C2**	**C3**	**X4**	**X5**	**X6**	**H7**	**H8**	**H9**
Bulk density(gm/ml)	0.488	0.456	0.506	0.456	0.403	0.516	0.395	0.503	0.488
Tapped density(gm/ml)	0.503	0.518	0.523	0.518	0.497	0.523	0.408	0.535	0.421
%Friability	0.602	0.518	0.512	0.617	0.528	0.512	0.598	0.421	0.512
Particle Analysis(gm retained on each sieve)									
16#	5.991	6.012	6.02	5.12	6.67	5.99	5.76	4.89	4.99
20#	0.372	0.265	0.245	0.287	0.176	0.201	0.344	0.412	0.356
24#	0.077	0.012	0.010	0.060	0.013	0.021	0.088	0.102	0.081
44#	0.055			0.003			0.021	0.037	0.022
Assay(%)	99	98.5	99.51	100.58	98.12	97.22	101.1	99.98	98.12

Parameters	**E10**	**E11**	**R12**	**R13**
Bulk density(gm/ml)	0.474	0.488	0.657	0.668
Tapped density(gm/ml)	0.504	0.503	0.702	0.712
%Friability	0.394	0.512	0.731	0.765
Particle Analysis(gm retained on each sieve)				
16#	5.121	4.76	5.02	5.16
20#	0.322	0.335	0.345	0.344
24#	0.041	0.022	0.065	0.071
44#	0.001	0.01	0.012	0.020
Assay(%)	97.01	97.17	96.5	99.01

Drug Release Profile: Formulation containing Carbopol 974P and Xanthan gum

Table 1.3: Drug Release Profile of Formulation Containing Carbopol 974P and Xanthan gum

Dissolution media	**Carbopol**	**%CDR**					
	Time(hr)	**C1** (carbopol-0.5%)	**C2** (carbopol-1%)	**C3** (carbopol-2%)	**X4** (xanthan gum-10%)	**X5** (xanthan gum-20%)	**X6** (xanthan gum-30%)
0.1N HCL	0.5	0	0	0	86.4	75.6	70.3
	1	0	0	0	122.44	112.02	98.89
	2	0	0	0	-	114.44	105.66
Phosphate buffer pH 6.8	3	66.6	63	0			
	4	108.72	108.35	77.4			
	5	-	-	113.83			

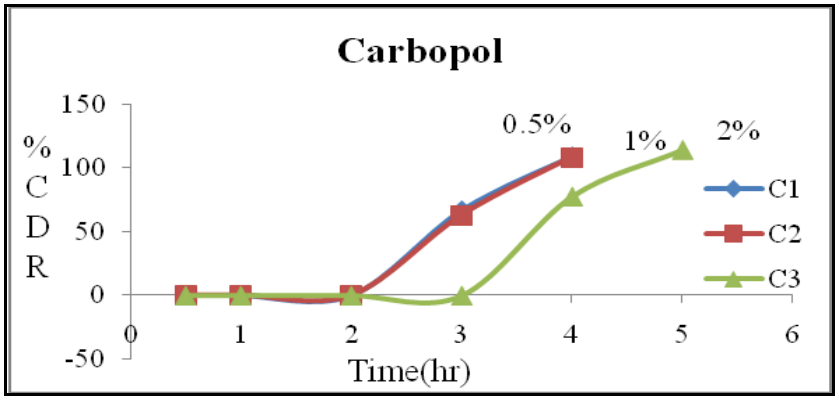

Figure 1.2: Drug Release Profile of Formulation Containing Carbopol 974P

Large size pellets were produced using carbopol 974P which were out of the range. Drug was not released till 3 hours, but when the pellets come in contact with pH 6.8, carbopol swell and all the drug is released within 4th hour in all three batches.

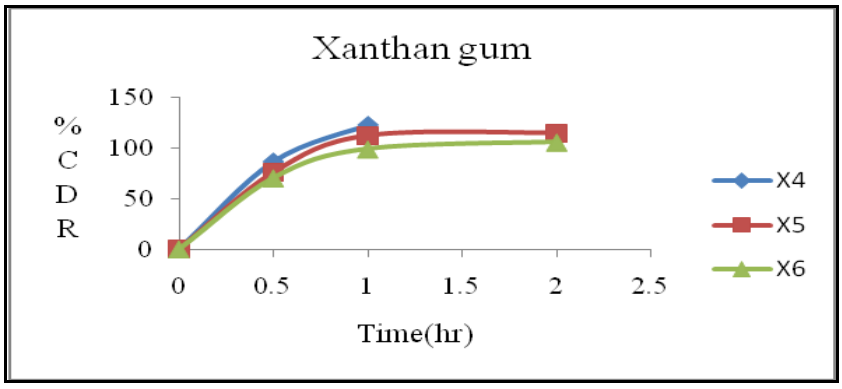

Figure 1.3: Drug Release Profile of Formulation Containing Xanthan gum

Appearance of pellets was good. It does not retard the drug release for more than 2 hours. Total drug release was achieved in 1st hour in X4(xanthan gum-10%) and X5(xanthan gum 20%). Total drug release was achieved in 2st hour in X6 (xanthan gum-30%). Xanthan gum is natural gum which may produce microbial growth during storage.

Dissolution profile: Formulation Containing HPMC K 100M and Ethyl cellulose

Table 1.4: Drug Release Profile of Formulation Containing HPMC K100 M and EC

Dissolution media	**Time(hr)**	**%CDR**				
		H7 (HPMC K100 M-8%)	**H8** (HPMC K100 M-12%)	**H9** (HPMC K100 M-16%)	**E10** (EC-20%)	**E11** (EC-40%)
0.1 N HCl	0.5	52.5	51.6	55.18	39.6	5.625
	1	57.28	69.86	68.08	50.62	21.2
	2	66	80.88	70.88	59.9	53.4
Phosphate buffer pH 6.8	3	120	105.32	75.33	81.8	74
	4	-	-	90.2666	90.57	81.2
	5				100.04	86.52

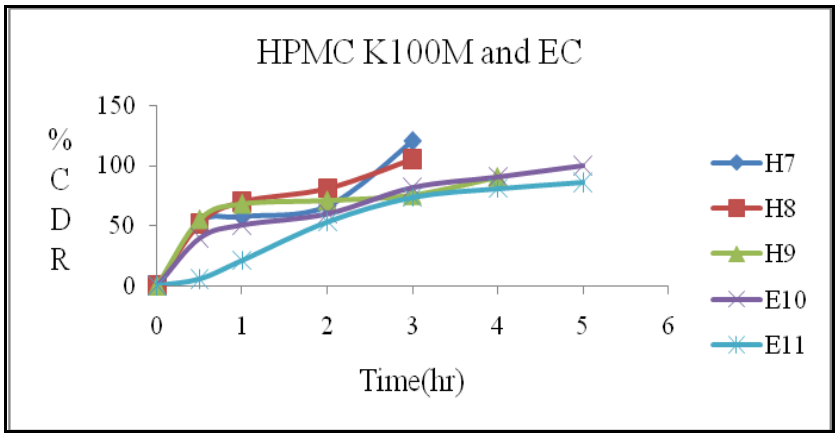

Figure 1.4: Drug release profile of batch containing HPMC K100M and EC

Description:

Batch H7 containing 8% HPMC K100M : It requires less time for spheronization. Total drug was released in 3 hours. Tramadol HCl is highly soluble in water and so only hydrophilic polymer can't retard the release.
Batch H8 containing 12% HPMC K100M: Total drug was released in 3 hours which is less than H5 batch. Required more time for spheronization than H5 batch.
Batch H9 containing 16% HPMC K100M: Required more time for spheronization than H7 and H8 batch. Total drug was released in 5 hours which is better than H7 and H8.
Batch E10 containing 20% EC: Total drug was released in 4th hour.
Batch E11 containing EC 40%: EC 40% produced a little brittle mass compare to EC 20%, but it sustained the release of drug for 5 hours. It did not give burst release. Gradually achieve loading dose within 1.5 hour. This shows better result compare to other polymer used before.

Dissolution profile: Formulation containing Eudragit RSPO

Table 1.5: Drug Release Profile of Formulation Containing Eudragit RSPO

Dissolution media	**Time(hr)**	**%CDR**	
		R10 (Eudragit RSPO-8%)	**R11** (Eudragit RSPO-15%)
0.1N HCl	0.5	50	52.1
	1	98	96.4
	1.5	110.2	109.3

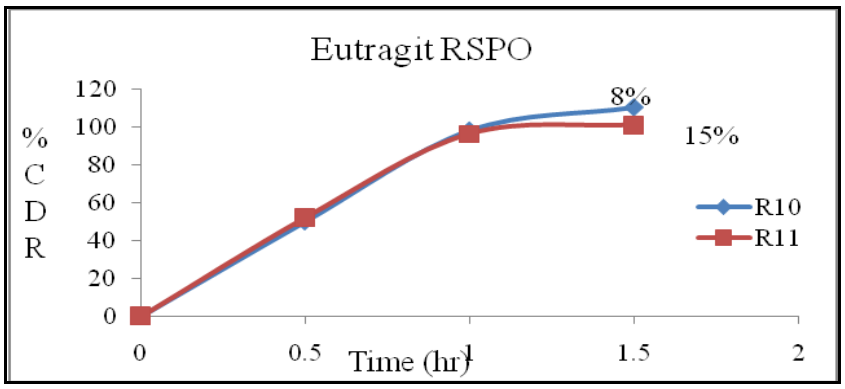

Figure 1.5: Drug Release Profile of Formulation containing Eudragit RSPO

2.Formulations to Optimize Two Polymers:

Combination of:HPMC K100M and EC
HPMC K100M and Eudragit RSPO
Carbopol and EC
HPMC K100M, EC and coating of Eudragit RSPO

Table 1.6: Formulation to optimize polymer combination: HPMC K100M and EC, HPMC K100M and Eudragit RSPO, Carbopol 974P and EC, HPMC K100M, EC and coating of Eudragit RSPO

Ingredients	**HE14**	**HR15**	**CE16**	**HEC17**
Drug Tramadol HCl (mg)	101.4	101.4	101.4	101.4
HPMC K100 M (%)	16	8	-	16
Carbopol 974P (%)	-	-	2	-
EC (%)	40	-	40	40
Eudragit RSPO (%)	-	15	-	-
MCC (%)	22	50	31	22
Lactose (%)	17	21	21	17
PVP k30 (%)	5	5	5	5
SSG (%)	1	1	1	1
Eudragit RSPO coating (%)	-	-	-	12

Evaluation:

Table 1.7: Evaluation of formulation to optimize polymer combination: HPMC K100M and EC, HPMC K100M and Eudragit RSPO, Carbopol 974P and EC, HPMC K100M, EC and coating of Eudragit RSPO

Parameters	**HE14**	**HR15**	**CE16**	**HEC17**
Bulk density(gm/ml)	0.474	0.398	0.355	0.488
Tapped density(gm/ml)	0.518	0.434	0.478	0.503
Particle Analysis(gm retained on each sieve)				
%Friability	0.421	0.407	0.512	0.512
16#	5.71	5.91	6.10	5.97
20#	0.387	0.268	0.275	0.388
24#	0.048	0.028	0.031	0.057
44#	0.031	-	-	0.003
Assay(%)	99.12	99.32	99.01	97.65

Dissolution profile:

Table 1.8: Drug Release Profile of Formulation Containing HPMC K100M and EC, HPMC K100M and Eudragit RSPO, Carbopol 974P and EC, HPMC K100M, EC and coating of Eudragit RSPO

Dissolution media	Time(hr)	%CDR			
		HE14	HR15	CE16	HEC17
0.1 N HCl		HPMC K100M 16% EC 40%	HPMC K100M 8% Eudragit RSPO 15%	Carbopol 974P 2% EC 40%	HPMC K100M 16%, EC 40% and coating of Eudragit RSPO (12%)
	1	24.75	45	42.94	36.2
	2	26.38	84	56.2	58.25
Phosphate buffer pH 6.8	3	37.58	106.2	88	74.99
	4	71.84	-	112.2	75.54
	5	84.46	-	-	77.56
	6	97.09	-	-	80.5
	7	118.86	-	-	81.9
	8				89.34
	9				96.5
	10				105.5

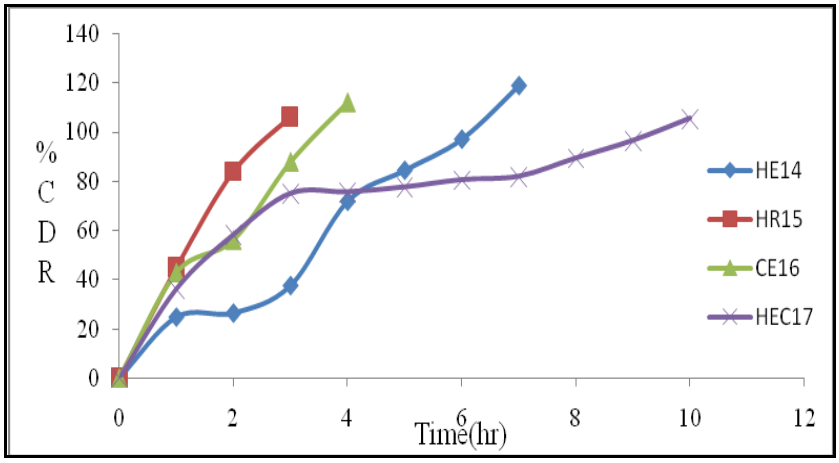

Figure 1.6: Drug Release Profile of combination polymers: HPMC K100M and EC, HPMC K100M and Eudragit RSPO, Carbopol 974P and EC, HPMC K100M, EC and coating of Eudragit RSPO

As Tramadol HCl is freely water soluble HPMC K100M and EC couldn't sustain the release. So coating of Eudragit RSPO was applied on pellets to achieve the goal of the sustaining the release till 12 hours. The result showed the drug release of 105% in 11 hours.

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. Carbopol 974P (Batch - C1 to C3), Xanthan gum (Batch - X4 to X6), HPMC K100M (Batch - H7 to H9) and EC (Batch - E10 & E11) alone are not capable of sustaining release up to 12 hrs. Combination of polymers (Batch - HE14, HR15, CE16) are used which do not sustained the release for 12hours. The optimum result was found by using HPMC K 100 M (16%), Ethyl cellulose (40%) and coating of Eudragit RSPO (12% and 15% weight gain). The optimized pellets (Batch HEC17) have sustained the drug release nearer to 12 hours and had produced pellets size in range. Assay and *In vitro* dissolution tests were performed for all the batches. 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 (16%), 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 nearer to 12 hours.

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