

FORMULATION AND EVALUATION OF BILAYER SUSTAINED RELEASE TABLETS OF TRAMADOL HYDROCHLORIDE BY USING NATURAL AND SYNTHETIC POLYMERS

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Abstract: The main objective of the present work was to develop sustained release bilayer tablets ofwater soluble drug tramadol using Guargum, HPMC, NaCMC and Xanthan gum, either alone or in combinations. Tablets were prepared by immediate release direct compression and sustained release wet granulation method and evaluated for various physical parameters. The drug release studies were performed using USP apparatus type I using 0.1N Hcl and pH 6.8 phosphate buffer as dissolution medium. The drug release was dependent on the type and concentration of the polymer. Drug release was faster from tablets prepared with Guargum, NaCMC and HPMC alone. However, in combination with HPMC, NaCMC, Guargum with Xanthan gum it sustained drug release effectively. The rate and mechanism of release of Tramadol Hcl analysed by fitting the dissolution data into the zero order, First order, Higuchi, Korsmeyer-Peppas and hexon crowel equations. All the Formulations (F1-F10) followed Zero order release Mechanism. Higuchi plots for all the formulations were linear indicating the drug release by diffusion controlled. Hixon-Crowell cube root model showed high r² value proportionality due to erosion of hydrophilic gel layer. To explore the release pattern, results of the in-vitro dissolution data were fitted to the Korsmeyer-Peppas equation, which characterizes the transport mechanism indicates the non fickian transport it refer to combination of both diffusion and erosion rate release. It can be concluded that the optimized batch F7 by adopting biphasic drug release pattern in a single dosage could improve patient compliance and give better disease management.

Keywords: Sustained release, Tramadol, Guargum, HPMC, Xanthan gum, Wet granulation

INTRODUCTION

The aim of this investigation is to Formulate and Evaluate the Sustain release Bilayer tablets of Tramadol Hcl using different synthetic and natural polymers. The concept of Bilayer tablet technology is utilized to develop sustains release and immediate formulation for a single drug or combination of drugs. Bilayer tablets are preferred in some cases because they maintain uniform drug levels, reduce dose, side effects, increase the safety margin for high-potency drugs and thus offer better patient compliance [35] Is a synthetic opiod analgesic Tramadol can be attributed to nor epinephrine and serotonin reuptake blockade in the cns, which inhibits pain transmission in the spinal cord. Tramadol Hcl possess short biological half life (5-7 hrs), patient should go for frequent administration usually thrice a day which might be a risk to the patient. In order to overcome this, Tramadol Hcl sustained release dosage forms are formulated ^[28]

Tramadol Hcl which is used as an analgesic is formulated as bilayered tablet which comprises of two layers among which the first layer is immediate release layer to provide immediate relief from pain and the second layer is sustained release layer to maintain steady state concentrations of drug in the blood. The current research is to formulate and evaluate an ideal bilayer matrix tablet of sustained release profile by using suitable methods by using different polymers.

MATERIALS AND METHODS

Tramadol hydrochloride, obtained from Spectrum pharma research solutions, Hyderabad, HPMCK100, Sodium Carboxy methyl cellulose, Xanthum gum, Guargum, Ethylcellulose, PEG-4000, Magnesium stearate, Sodium starch glycolate, Talc, Starch, Sodium hydroxide pellets, Potassium dihydrogen phosphate. All other excepients obtained from Loba Chemicals, Mumbai and SD Fine Chemicals limited, Mumbai.

Formulation of immediate release layer:

Direct Compression Method: The tablets were prepared by direct compression technique. Before blending of drug and other excipients, they were sifted through sieve no. 40 to remove any large particles. Drugs and other excipients were blended for 10 minutes. Then, subsequently this powder mixture was



blended for 5 minutes with talc. This mixture was directly compressed to get the tablets. The final weight of immediate release layer fixed to 84 mg^[2]

Formulation of sustained release layer:

Wet Granulation method: Drug and other excipients were sifted through sieve no. 40, blended uniformly and granulated with starch solution (10%) as granulating vehicle. The wet mass was prepared and passed through sieve no. 12. The granules were air dried for 10 minutes. And again passed through sieve no.24 Lubrication with sufficient quantity of talc was done and compressed into tablets. Ethyl cellulose was added between two layers. The final weight of sustained release layer fixed to 156 mg. 2 mg of Ethyl cellulose was added between two layers ^[3]

Drug–excipient compatibility studies: A Compatibility study focuses on a binary mixture of drug substance and some selected excipients in a fixed ratio with or without added moisture. The mixture stored at elevated temperatures as 40°c 75%RH, 55°C 60%RH in capped vials. The result of the interaction between the active drug and excipients is determined by FTIR.

Preformulation studies:

Colour and nature: Transferred small quantity of the sample on a white piece of paper, spreaded the powder and examined visually.

Taste and odour: Very less quantity of Tramadol Hcl was used to get taste with the help of tongue as well as smelled to get the odour $^{\rm [26]}$

Pre-compression characterization of blend:

Bulk density: A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume. Calculate the bulk density, in gm per ml, by the formula ^{[25].}

Tapped density: Tapped density is the ratio of mass of powder to the tapped volume.

Angle of repose: It is defined as the maximum angle is possible between the surface of the pile of the powder and the horizontal plain^[25].

Compressibility Index: The compressibility Index is measures of the propensity of powder to be compressed.

Hausner Ratio: It is the ratio of volume of tapped volume or tapped density to bulk density.

Evaluation of bilayer tablet:

Hardness: Tablet hardness has been defined, as the force required breaking a tablet a diametric

compression test. Hardness was measured by hardness tester.

Friability test: Weighed amount of 20 dedusted tablets were subjected to rotating chamber of "Roche type friability"^[25]

$$F = \frac{W_o - W}{W_o} x100$$

Disintegration time: Equivalent to 10mg of Tramadol was accurately weighed from powdered bilayered tablets and it was dissolved in distilled water to form a clear solution. One ml of the sample was withdrawn, suitably diluted with pH 6.8 phosphate buffer respectively and analysed spectrophotometrically at 272 nm respectively^[34-36]

In vitro dissolution Studies:

For immediate release layer Dissolution rate was studied by using USP type-I apparatus at 75 rpm using 900ml of 0.1 N HCl solutions as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5°C, aliquot of 5 ml of dissolution medium was withdrawn at every 15 min interval the absorbance of solution was measured by UV spectrophotometric method at 272nm and concentration of the drug was determined from standard calibration curve. The volume of the dissolution medium was adjusted to 900ml at every sampling time by replacing 5 ml with same dissolution medium^{[33,7,6].}

The in vitro release of drug from sustained layer was carried out for 10 hours using basket type tablet dissolution apparatus USP type-I containing 900 ml of dissolution medium maintained at 37±0.5°C and speed of agitation at 75 rpm. Using 900 ml of pH 6.8 phosphate buffers as a dissolution medium. ^{[33, 4, 8].}

RESULTS AND DISCUSSION

The present work was carried out on the Formulation and Evaluation of Bilayered tablets of Tramadol HCL comprising of immediate release layer for sudden onset of followed by Sustained release layer to maintain the steady state concentrations of the drug. HPMC K100, Sod.CMC, Xanthum gum and guar gum polymers were used in this investigation. Calibration plots for Tramadol HCL shows good linearity indicating that selection UVof spectrophotometry method for estimation of above named drugs is correct.

The following parameters of bilayer tablets were within acceptable official IP limits Pre-compressional parameters of bilayer tablets are Bulk density and tapped density for the formulations were in the range of 0.32- 0.39 gm/ml and 0.40 - 0.49 gm/ml. The angle of repose for the formulations was found to be in the

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range of 24.47 $^{\circ}$ to 32.38 $^{\circ}$. Compressibility index and Hauser's ratio were in the range of 10.61 to 13.72 % and 1.12 to 1.23., indicated that granules prepared by wet granulation method were free flowing.

The Evaluation of bilayer tablets (hardness, friability, weight variation, thickness, drug content, disintegration time) were within the acceptable official IP limits .The best formulation of bilayer tablets were selected for FTIR studies did not show any interaction between the polymer and pure drug.

The results of *in-vitro* drug release profile of Bilayer tablets depicts that combinations of natural gums play important role in the retardation and optimization of the drug release and increases the retardation of drug release from the SR layer of a Bilayer tablet. All formulations were prepared for IR layer by using sodium starch glycolate, PEG, Talc; the percentage drug release shows formulations (F1-F10) in the range of 98.289% to 99.897% for F7 and F3.

The rate and mechanism of release of Tramadol Hcl from the prepared bilayer tablets were analysed by fitting the dissolution data into the zero order, First order, Higuchi, Korsmeyer-Peppas and hexon crowel equations. All the Formulations (F1-F10) followed Zero order release Mechanism. Higuchi plots for all the formulations were linear indicating the drug release by diffusion controlled.

The erosion model was applied to *in vitro* release data, the linearity was observed with r value and also Hixon-Crowell cube root model showed high r^2 value of 0.949 to 0.989 suggested that the geometrical shape of tablet diminished proportionality due to erosion of hydrophilic gel layer.

To explore the release pattern, results of the invitro dissolution data were fitted to the Korsmeyer-Peppas equation, which characterizes the transport mechanism. The value of release exponent (n) for all formulations were in between 0.427 to 0.669 indicates the non fickian transport or anomalous diffusion it refer to combination of both diffusion and erosion rate release.

CONCLUSION

The present study was carried out to develop bilayered matrix tablets of Tramadol HCL Immediate release layer by direct compression method and hydrophilic polymes for sustain release layer by wet granulation method. Concluded that, the bilayer tablet technology can be successfully applied for Tramadol — HCL using of polymers such as HPMC K 100, Sod.CMC, Xanthum gum, Guar gum can be used as rate controlling polymers by appropriate selection of the level of polymers in the matrix tablets. It can be

concluded that the optimized batch F7 by adopting biphasic drug release pattern in a single dosage could improve patient compliance and give better disease management.

Table no.1:	Composition	of IR	layer	of	Bilayered	tablets
prepared by	Direct Comp	oressio	n tech	nnio	que	

S.no	Ingredients	Composition (mg)
1	Tramadol	50
2	Sodium starch glycolate	25
3	PEG	10
4	Talc	2
5	Magnesium stearate	2
6	Ethyl cellulose	2

Table no.2: Composition of SR layersof Bilayered Tablets
prepared by Wet Granulation technique

Formulation	F1	F ₂	F ₃	F_4	F ₅	F ₆	F ₇	F ₈	F9	F ₁₀
	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)
Tramadol	100	100	100	100	100	100	100	100	100	100
Hcl										
Gum gum	50	-	-	-	25	-	25	25		-
Xanthum	-	50	-	-	-	25	25	-	25	-
gum										
HPMC	-	-	50	-	25	25	-	-		25
NA CMC	-	-	-	50	-	-	-	25	25	25
Starch (10%)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Mg stearate	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3
Total wt	156	156	156	156	156	156	156	156	156	156

Table no: 3: Calibration curve for tramadol hcl in ph 6.8:

S.No	Concentration(µg/ml)	Absorbance(272 nm)
1	0	0
2	2	0.012
3	4	0.022
4	6	0.034
5	8	0.043
6	10	0.055
7	12	0.066

Table no.4: Evaluation of Tramadol Hcl bilayer tablets ofTramadol Hcl

Formulation	Hardness (kg/cm³)	Wt. variation (mg)	Thickness (cm)	% Fribility	In vitro disintegration time (sec)
F1	5.23 ± 0.18	241.3 ± 2.45	5.31 ± 0.31	0.59 ± 0.21	50.1 ± 4.15
F2	5.4 ± 0.22	240 ± 1.56	5.28 ± 0.18	0.51 ± 0.17	52.9 ± 3.93
F3	5.32 ± 0.25	240.7 ± 0.94	5.2 ± 0.18	0.48 ± 0.18	45.2 ± 4.68
F4	5.33 ± 0.26	239.2 ± 2.85	5.22 ± 0.20	0.55 ± 0.21	36 ± 2.75
F5	5.54 ± 0.12	239.7 ± 2.00	5.07 ± 0.36	0.47 ± 0.47	55.1 ± 2.58
F6	5.3 ± 0.18	240.3 ± 1.33	4.99 ± 0.28	0.61 ± 0.13	65 ± 2.28
F7	5.36 ± 0.24	240 ± 1.41	5.06 ± 0.25	0.59 ± 0.24	70.1 ± 2.91
F8	5.37 ± 0.23	240.6 ± 1.34	5.06 ± 0.30	0.64 ± 0.17	57 ± 3.54
F9	5.54 ± 0.14	239.6 ± 3.27	5.12 ± 0.35	0.64 ± 0.25	61.3 ± 5.15
F10	5.4 ± 0.16	239.7 ± 1.88	5.21 ± 0.28	0.63 ± 0.17	54.6 ± 2.10

Table no.5: Cumulative percent drug release data for bilayer tablet for Sustained release

s.no	TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
	(hr)	G	Х	H	N	(G+H)	(X+H)	(G+X)	(G+N)	(X+N)	(H+N)
1	0.5	25.34	22.11	33.969	35.476	27.874	27.75	22.11	30.589	29.865	34.571
2	1	33.666	24.12	41.406	46.698	35.838	35.684	24.135	36.924	38.734	40.725
3	1.5	34.571	31.356	49.647	59.006	42.354	42.532	27.135	43.078	48.508	48.689
4	2	46.155	40.401	60.702	75.115	51.947	49.199	33.768	46.979	52.128	53.938
5	2.5	53.576	49.446	71.556	86.88	59.549	56.227	41.808	51.766	58.101	59.549
6	3	59.73	57.285	80.802	95.568	69.142	57.669	47.258	59.766	62.264	67.513
7	3.5	69.142	63.114	88.641	97.016	76.02	64.156	51.225	68.599	68.056	73.486
8	4	77.106	76.179	91.656	99.369	80.907	68.120	53.265	77.468	72.038	81.812
9	4.5	86.518	82.209	96.279		85.251	70.102	59.898	83.079	74.029	86.699
10	5	93.396	85.626	99.897		57.242	72.445	66.933	86.699	79.278	94.301
11	5.5	95.93	93.063			89.957	76.049	70.725	89.957	82.536	97.921
12	6	99.188	95.676			95.749	81.815	75.174	93.034	87.423	98.645
13	6.5		97.083			97.921	84.879	78.792	95.568	90.138	
14	7		99.495			98.826	89.744	82.611	98.102	91.948	
15	7.5						92.627	85.827		93.396	
16	8						95.330	89.455		95.568	
17	8.5						98.295	93.465		97.921	
18	9						99.295	96.078		99.731	
19	9.5							98.289			
20	10							99.696			

Table no.6: Mechanism of drug release

S.no	Formulation	Zero	First	Higuchi	Peppas	Hixon
		order	order	(R)*	(R)*	crowel
		(R) ²	(R) ²			(R) ²
1	F1	0.972	0.831	0.968	0.961	0.949
2	F2	0.966	0.858	0.966	0.964	0.971
3	F3	0.927	0.741	0.991	0.978	0.959
4	F4	0.909	0.928	0.986	0.980	0.989
5	F5	0.916	0.917	0.992	0.987	0.987
6	F6	0.922	0.841	0.966	0.995	0.959
7	F7	0.971	0.792	0.982	0.968	0.953
8	F8	0.936	0.929	0.985	0.965	0.983
9	F9	0.890	0.829	0.993	0.997	0.973
10	F10	0.932	0.874	0.989	0.971	0.961



Figure no.2: FT-IR Spectrum of Tramadol Hcl with xanthum and guar gum







Figure no.4: In-vitro Drug Release Kinetics for Bilayered Tablets

Graphs for F-7 formulation:



Figure no: 5



Figure no: 6



Figure no: 7



Figure no: 8

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