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Original Article

Formulation and Evaluation of Immidiate Release and Sustained Release Bilayer Tablets of Tramadol Hydrochloride

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ABSTRACT

Tramadol is a centrally acting analgesic having amino cyclo hexanol group, which has a strong analgesic action .It is administered when non steroidal anti inflammatory drugs fail to mitigate pain. Conventional sustained release formulation of Tramadol hydrochloride is not adequate because of lack of initial bolus dose. This drawback can be overcome by combining immediate release and sustained release in a single bilayer tablet. Hence, the aim of the current work is to develop a bilayer dosage form which would release 30% of the drug within 30 minutes and the balance 70% would then release over a period of 12 to 24 hours. In order to optimize the various parameters six different formulations of IR layer and twelve different formulations of SR layer were prepared and compressed separately . The best formulation for both IR nd SR layer selected on the basis of their dissolution profiles. A tablet press had been specifically designed and developed for the production of bilayer tablets. From the study it was concluded that bilayer tablets of Tramadol Hydrochloride can be successfully formulated with 4% crosspovidone as superdisintegrant for immediate release layer and 25% HPMC K 100M and 25% PEO N80 as polymers for sustained release layer. The percentage drug release of the optimized batch was found to be 97.51% at 24th hour. Thus bilayer tablets could be a potential dosage form for delivering Tramadol as immediate release and controlled release manner.

Keywords: Tramadol, Bilayer tablet, Immidiate Release, Sustained Release.

INTRODUCTION

Tramadol is a centrally acting analgesic having amino cyclo hexanol group, which has a strong analgesic action. It acts as a opiod agonist through selective

binding to μ-opiod receptots, releases serotonin and inhibits the reuptake of norepinephrine. It is administered when non steroidal anti inflammatory drugs fail to mitigate pain[1]. Conventional sustained release formulation of Tramadol hydrochloride is not adequate because of lack of initial bolus dose. This drawback can be overcome by combining immediate release layer and sustained release layer in a single bilayer tablet[2]. By developing such novel formulation it is possible to reduce the frequency of administration, to avoid dose related risks, to avoid shortcomings of a single layer tablet and improve patient compliance.

In developing a sustained release dosage form for Tramadol, it is important to have a fast release fraction which would allow for sufficient concentration of the drug in the blood stream to produce quick analgesic effect and a slow release fraction which would maintain that effect. Hence, the aim of the current work is to develop a bilayer dosage form which would release 30% of the drug within 30 minutes and the balance 70% would then release over a period of 12 to 24 hours. In order to optimize the various parameters six different formulations of IR layer and twelve different formulations of SR layer were prepared and compressed separately. The best formulation for both IR nd SR layer selected on the basis of their dissolution profiles[3]. The target product profile is given in Table 1. Various concentrations of crosspovidone were used to optimize the IR- layer and different grads of HPMC (K100M) and PEO N80 were used to optimize the SR-layer.

A tablet press had been specifically designed and developed for the production of bilayer tablets[3] and provides displacement weight monitoring for accurate and independent weight control of the individual layers, low compression force exerted on the first layer to avoid capping and separation of the two individual layers, increase dwell time at precompression of both first and second layer to provide sufficient hardness at maximum turret speed, maximum prevention of cross contamination between the two layers, a clear visual separation between the two layers.

MATERIALS AND METHODS

Chemicals and Reagents

Tramadol Hydrochloride (Matrix Labs, Hyderabad), Hydroxy Propyl methyl cellulose K100M, Hydroxy Propyl methyl cellulose K15M, Sodium carboxy methyl cellulose , Hydroxy Propyl cellulose, Magnesium Stearate (Srinihal pharmachemicals,Hyderabad). All other chemicals and reagents used were of Analytical Reagent grade from Merck. Purified water USP was used where ever required.

Experimental

For IR-layer: Direct Compression[4]: All the ingredients were passed through 60 # screen prior to mixing. The sifted drug and polymers were accurately weighed and loaded into the octagonal blender in the ascending order. Sifted Lactose, Micro crystalline cellulose, Sodium starch glycolate[5] or Crosspovidone, Pregelatinised starch were mixed with equal quantity of blend in a polythene bag for a few minutes and added to the blender and lubricated for 10 mins at 8 RPM. Sifted Magnesium stearate was added to the blender and blended again for 5 minutes at 8 RPM. A total of six immediate release formulations were prepared and subjected to pre compression studies like Bulk density, Tapped density, Angle of repose, Compressibility Index, Hausner's Ratio before compression. The composition of the formulations is given in Table 2.

For SR-layer: Direct compression[6]: All the ingredients were passed through 60 # screen prior to mixing. The sifted drug and

polymers[7] were accurately weighed and loaded into the octagonal blender in the ascending order. Sifted Sodium carboxy methyl cellulose, Povidon K 30, Colloidal silicon dioxide, Micro crystalline cellulose, Polyethylene oxide were mixed with equal quantity of blend in a polythene bag for a few minutes and added to the blender and lubricated for 10 mins at 8 RPM. Sifted Magnesium stearate was added to the blender and blended again for 5 minutes at 8 RPM A total of twelve sustained release formulations were prepared and subjected to pre compression studies like Bulk density, Tapped density, Angle of repose, Compressibility Index, Hausner's Ratio before compression. The composition of the formulations is given in Table 3.

The in vitro dissolution profile was conducted in 0.1 N HCL , PH 1.2[8] for all the prepared IR batches for 10, 15, 30 and 45 mins and for all the twelve SR formulations prepared the dissolution medium used was 0.2 M Phosphate buffer and samples were withdrawn at 1,2,4,6,8,10,12,16 and 24 hours in USP Type II apparatus[9] and analyzed for % drug dissolved using UV spectrophotometric method. The best formulation for IR and SR layers chosen on the basis of the result of dissolution studies and compressed together in order to prepare a bilayer tablet.

Bilayer tablets of 400mg weight were prepared by the direct compression[10] (IR and SR-layer)[11] methods. The composition is given in Table 4.

Bilayer tablets were compressed using 12mm punch in a 16 station rotary tablet machine with double feed by direct compression technique and evaluated. The physical properties and assay values for all batches are given in Table 5.

RESULTS & DISCUSSION

All the 12 SR formulations and six IR formulations prepared showed the bulk density between 0.35 to 0.53gm/cm^3, compressibility index should be < 26, but in case of SR Formulations SF1-SF6 and in case of IR formulations IF1-IF3, the particles produced exhibited poor flow properties, Hausner's ratio was found to be within the acceptable range of <1.35, Angle of Repose also was found to be acceptable i.e < 45 for all the prepared IR and SR formulations.

Results of dissolution profiles of various IR formulations showed that formulations IF6 showed 98% drug release at the end of 45 minutes which is much more than all the other Immediate release formulations and may be due to increase in the amount of crospovidone and also 1:1 ratio of Lactose and Micro crystalline cellulose. Thus due to fast release of drug within the stipulated time IF6 was chosen as the best formulation.

Similiarily for all the twelve batches of SR formulations it was found that batch SF12 gives desirable sustained effect for 24 hours giving 97% drug release. Therefore formulation SF12 containing 25% HPMC K 100M and 25% of PEO N 80 was chosen as the best formulation.

The Average weight, Hardness, Thickness, Friability, Drug content and Disintegration time of the compressed bilayer tablet were within the acceptable range. When subjected to dissolution studies as shown in Figure 1, IR layer disintegrated with immediate release of the drug within 30 mins with simultaneous imbibition of dissolution medium by the tablet with the formation of gel layer by the polymers HPMC K 100 M and PEO N80 which swell when in contact with the dissolution medium thereby leading to the formation of a thicker gel layer with a decrease in the drug release. Hence it can be concluded that Biphasic release of Tramadol Hydrochloride had been achieved due to addition of proper proportion of crospovidone in the IR layer and rate retarding polymer in the SR Layer.

CONCLUSION

The present study was undertaken with an aim to design oral immediate release and sustained release bilayer tablet of Tramadol Hydrochloride. Results indicated that release of the drug from the tablet was influenced by content of superdisintegrant and polymer matrices. Formulation containing 4% crosspovidone as superdisintegrant for immediate release layer and 25% HPMC K 100M and 25% PEO N80 as polymers for sustained release layer showed desired drug release. So, bilayer tablets could be a potential dosage form for delivering Tramadol Hydrochloride. Success of the *In vitro* drug release studies recommends the product for further in vivo studies.

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Table 1. Target Product Profile

S. NO.	PARAMETERS	SPECIFICATIONS
	Discription	White and red colour round shape bilayer tablet with immediate release Tramadol 125mg in one layer and sustained release Tramadol 275mg in another layer
1	Average weight	400mg
2	Content Uniformity	99.26%
3	Hardness	6.21 kg/cm2
4	Friability	0.45%w/w
5	Disintegration time of IR layer	9.34 secs
6	Thickness	4.53mm
	Dissolution testing for Bilayer tablet (0.1 N HCL, PH 1.2)	
	Time	Cumulative % Drug Released
	10 mins	25
	15 mins	27
	30 mins	32
	45 mins	39
	Dissolution testing for Bilayer tablet (0.2 M Phosphate buffer)	
	1 hour	46
	2 hour	54
	4 hour	65
	6 hour	69
	8 hour	72
	10 hour	78
	12 hour	83
	16 hour	91
	24 hour	98

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Table 2. Composition of the Immidiate Release Formulations (mg/Tablet)

Ingredients	IF1	IF2	IF3	IF4	IF5	IF6
Tramadol	50	50	50	50	50	50
Crosspovidone	-	5	5	5	7.5	7.5
L Hydroxy Propyl Cellulose	2.75	2.75	2.75	2.75	2.75	2.75
Lactose	33	33	66		31.75	31.75
Micro crystalline Cellulose	33	33	-	66	-	31.75
Magnesium stearate	1	1	1	1	1	1
Iron oxide red	0.25	0.25	0.25	0.25	0.25	0.25
Pre gelatinized starch	-	-	-	-	31.75	-
Sodium starch glycolate	5	-	-	-	-	-
Total weight	125	125	125	125	125	125

Table 3. Composition of the Sustained Release Formulations (mg/Tablet)

Ingredients	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9	SF10	SF11	SF12
Tramadol HcL	100	100	100	100	100	100	100	100	100	100	100	100
Hydroxy Propyl Methyl Cellulose K15	100	125	150	100	100	-	-	-	-	-	-	-
Hydroxy Propyl Methyl Cellulose K100	-	-	-	-	-	100	125	150	75	-	75	75
Sodium carboxy methyl cellulose	-	-	-	50	-	-	-	-	75	75	50	-
Poly ethylene oxide N80	-	-	-	-	50	-	-	-	-	50	-	50
Povidone K 30	5	5	5	5	5	5	5	5	5	5	5	5
Micro crystalline Cellulose	40	15	15	15	15	40	15	15	15	15	15	15
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Colloidal silicon dioxide	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	275	275	275	275	275	275	275	275	275	275	275	275

Table 4. Composition of the Bilayer tablet (mg/Tablet)

Ingredients	IR Formulation Batch (IF6)	IR Formulation Batch (SF12)	Bilayer Tablet (BF)
Tramadol	50	100	150
Crosspovidone	7.5	-	7.5
L HPC	2.75	-	2.75
Lactose	31.75	-	31.75
Micro crystalline Cellulose	31.75	15	46.75
Magnesium stearate	1	2.5	3.5
Iron oxide red	0.25		0.25
HPMC K 100	-	75	75
Poly ethylene oxide N80	-	75	75
Povidone K30	-	5	5
Colloidal silicon dioxide	-	2.5	2.5
Total weight	125	275	400

Table 5. Evaluation of the prepared Bilayer tablet

Formulation	Hardness (kg/cm2)	Thickness (mm)	Weight variation (mg)	Friability (%w/w)	Content Uniformity (%)	Disintegration Time (min.sec)
	6.21	4.53	1.91	0.45	99.26	9.34

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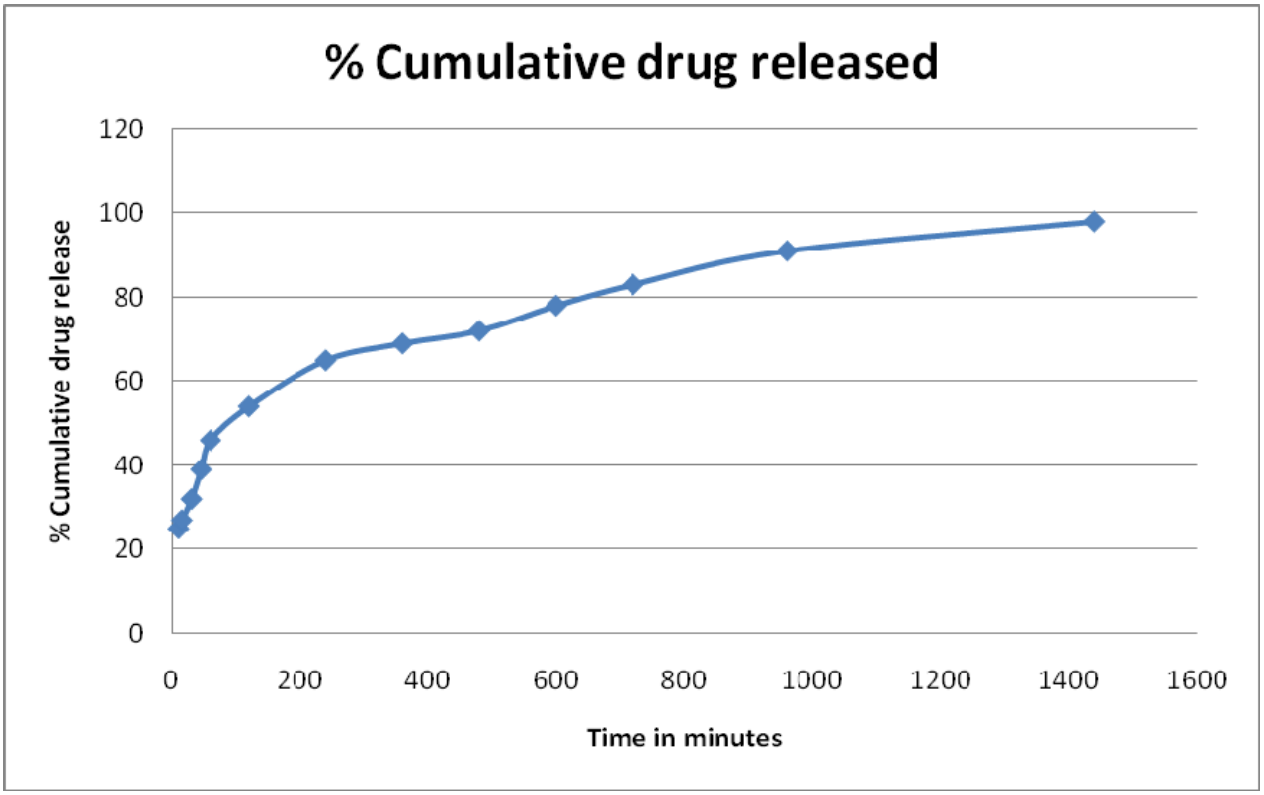

Figure.1. Graphical representation of dissolution profile of Bilayer tablet of Tramadol Hcl