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FORMULATION AND IN VITRO EVALUTION OF SUSTAINED RELEASE TABLETS OF CLOMIPRAMINE HYDROCHLORIDE

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ABSTRACT

Current state of art is witnessing a revolution in new techniques for drug delivery. Nevertheless, convenience of manufacturing and patient compliance has maintained their significant importance in the design of drug delivery systems. The objective of the project was to develop a stable and robust formulation of the clomipramine hydrochloride. The present study deals with evaluation and optimization of various critical formulation and process variables of oral solid sustained release dosage form, containing an anti-depressant clomipramine hydrochloride drug. Clomipramine was having extensive 1st pass metabolism and associated with frequent dosing of conventional dosage form makes it a suitable candidate for sustained release dosage form for patient compliance. For present work, eudragit having different grades like RL 30D, RS 30D were selected as release retarding agent. Matrix system of clomipramine hydrochloride based on hydrophobic polymer (eudragit RL 30D, eudragit RS 30D, etc.) was tried individually as well as in combinations. Finally core tablets were coated using HPMC 6 Cps. Final optimized batches (F011) obtained fulfilled the criteria of significantly retard the release up to 24 hours with initial loading dose release. Thus it was considered as the optimized batch for once a day sustained release tablet formulation containing clomipramine hydrochloride.

Keywords: Clomipramine hydrochloride, eudragit RL 30D, eudragit RS 30D, HPMC 6 Cps, sustained release tablets.

INTRODUCTION

Obsessive-compulsive disorder (OCD) traditionally has been considered a rare, treatment refractory disorder of psychological origin. However, OCD appears to be much more common than was previously believed. Moreover, in recent years controlled studies demonstrated that clomipramine is more effective than placebo and than other tricyclics for reducing obsessive-compulsive symptoms. Although it has been suggested that clomipramine was effective in treating obsessive-compulsive symptoms by an antidepressant mechanism, the majority of the controlled studies found that its

antiobsessional effects occurred whether the patient was depressed or not. The apparent specificity of clomipramine, and, to some extent, newer serotonin selective antidepressants, suggests a serotonergic role in the psychobiology of OCD.[1-6] The primary objective of sustained drug delivery system is to ensure safety and to improve the patient compliance as well as efficacy of the drugs and this can be achieved by less frequent dosing and better control of drug plasma level. The sustained release formulation is frequently necessary for chronic drug administration such as the use of antipsychotic, antidepressants, antihypertensive, antidiabetics, and for the management of psychosis, depression, hypertension, and diabetes respectively. Clomipramine hydrochloride is a tricyclic Antidepressant specifically 5-HT receptor blocker useful in the treatment of Obsessive Compulsive Disorder (OCD) and Depressant. Clomipramine hydrochloride has been classified as a class 1 substance according to biopharmaceutics classification system (BCS), meaning that it is highly soluble and highly permeable. The present research endeavor was directed towards the development of sustained release dosage form of Clomipramine hydrochloride in the form of tablets to be taken once a daily.

MATERIALS AND METHODS

Materials

Clomipramine hydrochloride was a gift from R.L fine chemicals (Bangalore India). Ethylcellulose (14 cps) was purchased from SD Fine Chemicals Ltd (Mumbai India). Eudragit RL and Eudragit RS were procured from Rohm Pharma (Weiterstadt, Ger-many). All the other chemicals used were of high analytical grade.

Methods

Preparation of Tablets

Different tablet formulations were prepared by wet granulation technique. All the powders were passed through 80 #. Required quantities of drug and polymer were mixed thoroughly, and a sufficient volume of granulating agent (DCP dihydrate, aerosil, HPMC 6 cps, eudragit RL 30D eudragit RS 30D) was added slowly. After enough cohesiveness was obtained, the mass was sieved through 22/44 mesh. The granules were dried at 55°C for 1 hour. Once dry, the granules retained on 44 # were mixed with 15% of fines (granules that passed through 44 #). Aerosil and calcium stearate were

finally added as glidant and lubricant. The practical weight of tablets was calculated based on the drug content of the granulations, and the tablets were compressed (12x 5.5 capsule, breakline on both sides) using a single-punch tablet compression machine (Cadmach, Ahmedabad, India). Each tablet contained 75 mg of clomipramine hydrochloride and other pharmaceutical ingredients prior to the compression, the granules were evaluated for several tests.

Evaluation of Granules

Angle of Repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation[7-11] :

$\tan \theta = h/r$ (1)

where h and r are the height and radius of the powder cone.

Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formula [12,13] :

LBD = weight of the powder/volume of the packing (2)

TBD = weight of the powder/tapped volume of the packing (3)

Compressibility Index

The compressibility index of the granules was determined by carr's compressibility index[14-16]:

Carr's index (%) = [(TBD – LBD) × 100]/TBD (4)

Drug Content

An accurately weighed amount of powdered clomipramine hydrochloride granules (100 mg) was extracted with water and the solution was filtered through 0.45µ membrane (nunc, new delhi, india). The absorbance was measured at 262 nm after suitable dilution.

Evaluation of Tablets[17-19]

Thickness

The thickness of the tablets was determined using a thickness gauge (mitutoyo, new delhi, india). Five tablets from each batch were used, and average values were calculated.

Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (denver APX-100, arvada, colorado), and the test was performed according to the official method.

Hardness and Friability

For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto hardness tester (cadmach, ahmedabad, india) and the roche friabilator (campbell electronics, mumbai, india), respectively.

TABLE 1: BATCH COMPOSITION FOR FORMULATION F1 TO F4

Batch No.	**F1**	**F2**	**F3**	**F4**
Ingredients	**Qty/Tab (mg)**	**Qty/Tab (mg)**	**Qty/Tab (mg)**	**Qty/Tab (mg)**
Clomipramine HCl	75.0	75	75.0	75
DCP Dihydrate	-	-	-	-
DCP Dihydrate (granular)	204.5	226.5	204.5	204.5
Aerosil	3.5	-	-	-
HPMC 6 cps	-	-	-	-
Eudragit RL 30D	22.7	-	-	-
Eudragit RS 30D	-	19.29	22.7	31.5
P. water				
DCP Dihydrate (granular)	32	-	32	32

Aerosil	3.5	3.5	3.5	3.5
Calcium stearate	3.5	3.5	3.5	3.5
Tablet weight	**344.8 mg**	**327.79 mg**	**341.2 mg**	**350 mg**
SR Coating				
Eudragit RL 30D	-	-	-	-
Eudragit RS 30D	-	3.41	-	-
Talc	-	0.52	-	-
Tri ethyl citrate	-	0.341	-	-
P. water				
Film Coating				
HPMC 6 cps	5.94	5.94	-	5.94
Iron oxide red	0.16	0.16	-	0.16
TiO2	1.82	1.82	-	1.82
Cremophore RH40	0.08	0.08	-	0.08
P. water	q.s	q.s		q.s
Total weight	**352.69 mg**	**340.1 mg**	**341.2 mg**	**358 mg**

TABLE 2: BATCH COMPOSITION FOR FORMULATION F5 TO F8

Batch No.	**F5**	**F6**	**F7**	**F8**
Ingredients	Qty/Tab (mg)	Qty/Tab (mg)	Qty/Tab (mg)	Qty/Tab (mg)
Clomipramine HCl	75	75	75	75
DCP Dihydrate	-	-	236.5	236.5
DCP Dihydrate (granular)	204.5	204.5	-	-
Aerosil	-	-	-	-
HPMC 6 cps	-	-	-	-
Eudragit RL 30D	-	-	-	-
Eudragit RS 30D	31.5	31.5	31.5	31.5
P. water				
DCP Dihydrate (granular)	32	32	-	-
Aerosil	3.5	3.5	3.5	3.5
Calcium stearate	3.5	3.5	3.5	3.5
Tablet weight	**350 mg**	**350 mg**	**350 mg**	**350 mg**
Film coating				
HPMC 6 cps	5.94	-	5.94	5.94

Iron oxide red	0.16	-	0.16	0.16
TiO2	1.82	-	1.82	1.82
Cremophore RH40	0.08	-	0.08	0.08
P. water	q.s		q.s	q.s
Total weight	**358 mg**	**350 mg**	**358 mg**	**358 mg**

TABLE 3: BATCH COMPOSITION FOR FORMULATION F9 TO F11

Batch No.	**F9**	**F10**	**F11 (optimized batch)**
Ingredients	Qty/Tab (mg)	Qty/Tab (mg)	Qty/Tab (mg)
Clomipramine HCl	75	75	75
DCP Dihydrate	-	-	-
DCP Dihydrate (granular)	204.5	204.5	204.5
Aerosil	-	-	-
HPMC 6 cps	-	-	-
Eudragit RL 30D	-	-	-
Eudragit RS 30D	31.5	31.5	31.5
P. water			
DCP Dihydrate (granular)	32	32	32
Aerosil	3.5	3.5	3.5
Calcium stearate	3.5	3.5	3.5
Tablet weight	**350 mg**	**350 mg**	**350 mg**
Remarks	-	-	-
HPMC 6 cps	8	8	8
Iron oxide red	0.16	0.16	0.16
TiO2	1.82	1.82	1.82
Cremophore RH40	0.08	0.08	0.08
P. water	q.s	q.s	q.s
Total weight	**360.06 mg**	**360.06 mg**	**360.06 mg**

RESULTS AND DISCUSSION

Dissolution Profile for Trial Batches

Dissolution Medium: 1 hr in 0.1 N hydrochloric acid followed by pH 6.8 Phosphate buffer for rest of the 23 hrs.

TABLE 4: % DRUG RELEASE FOR BATCHES F001 TO F004

Time (hr)	F001 n=3	F002 n=3	F003 n=3	F004 n=3
1	46.8±1.43	23.5±0.98	51.5±1.11	51.9±2.29
2	69.6±3.06	32.8±2.71	84.3±1.98	75.1±3.02
4	80.0±2.05	34.1±3.02	86.9±3.01	79.4±1.73
6	82.8±1.32	38.3±2.64	90.0±2.31	81.5±2.77
8	85.6±2.08	39.3±2.97	92.2±1.03	82.8±3.12
10	87.2±2.81	44.1±3.02	94.1±2.67	83.8±2.36
12	89.9±3.02	43.8±1.49	95.3±2.93	83.9±1.76
18	90.5±2.11	48.9±3.11	96.2±2.42	84.8±3.17
24	91.8±1.76	51.7±2.16	95.4±0.96	86.8±3.01

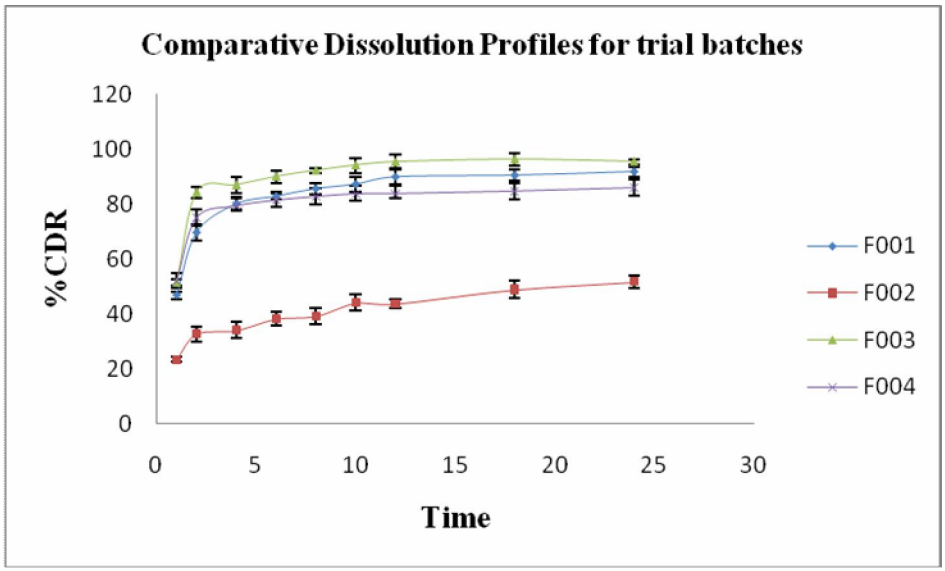

Figure1
Comparative Dissolution Profiles for Trial batches (F001, F002, F003 and F004).

In trial F001, DCP dihydrate's granular form was used & in place of eudragit RS 30D, eudragit RL 30D was used with decreasing in the quantity.

In trial F002, DCP granular form was continuing to use & eudragit RS 30D is used in the granulation as well as in the sustained release coating. But this gives very retardation of the dissolution profile.

In trial F003, reproducible batch of F004 was taken without coating of the tablets. These give almost reproducible results.

So in trial F004, granulation was decided to be done in the fluidized bed coater with top spray for effective & reproducible granulation. In this batch, 20% of eudragit RS 30D was used in the granulation step. First clomipramine & DCP granular were mixed in the RMG, than this blend was transferred to the FBC for granulation part. Here, some part of DCP granular was added to the extragranular part with aerosil & calcium stearate. Finally film coating of the tablet was done.

TABLE 5: % DRUG RELEASE FOR BATCHES F005 TO F008

Time (hr)	F005 n=3	F006 n=3	F007 n=3	F008 n=3
1	50.5±2.54	51.3±0.82	55.6±1.04	54.4±2.56
2	69.9±2.18	68.5±2.95	65.3±2.96	64.2±3.10
4	80.6±1.84	82.5±0.76	76.1±2.67	75.4±2.06
6	83.7±3.07	85.0±1.09	80.2±0.91	78.9±1.14
8	84.2±3.10	86.2±2.93	83.9±2.57	81.4±2.97
10	87.0±2.08	87±1.55	86.3±1.04	85.8±2.65
12	87.6±1.92	87.9±1.64	89.7±3.10	88.4±3.03
18	88.4±1.51	88.7±0.98	94.3±1.86	92.7±1.34
24	90.3±0.99	91.3±1.27	97.6±2.94	98.6±0.78

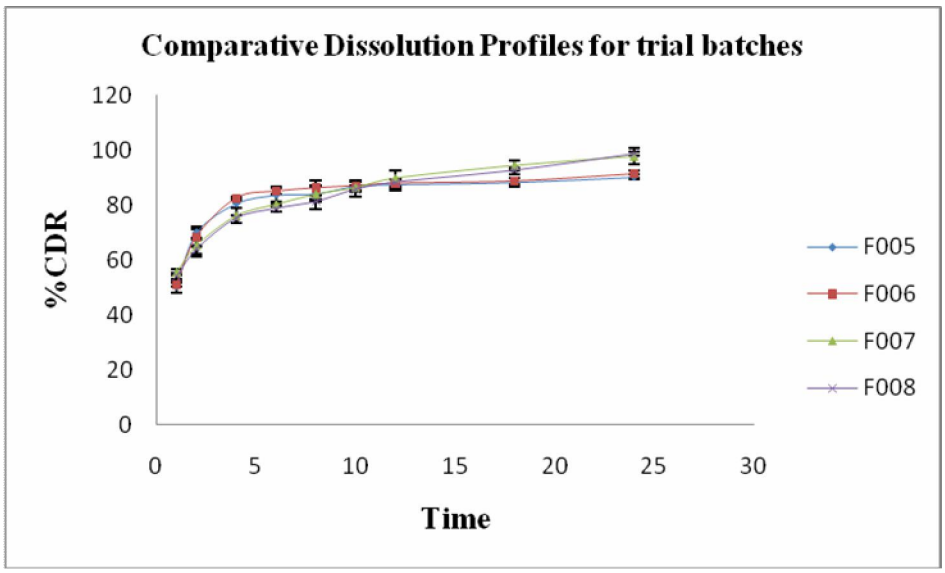

Figure 2
Comparative Dissolution Profiles for Trial batches (F005, F006, F007 and F008).

The trial F005 was the reproducible batch of trial F004 with taking care to increase the assay of the blend. So for this, 10% solution of the eudragit was taken for wetting of the drug & DCP granular part. Remaining part of the solution was taken in the granulation part. Assay was less in this batch also

Trial F006 was the reproducible batch of the F004. But in this batch, assay was 84% due to higher initial fluidization in the FBC. Due to this, drug loss occurs. So this batch was not compressed in to the tablets & batch discontinued.

In the trial F007, DCP dihydrate-fine powder was used in place of DCP granular form. Whole quantity of DCP was used in the granulation part, not in the extragranular part.

Trial F008 was the reproducible batch for F007 for checking the assay. Assay of both the batches obtained almost same. So both the batches were compressed & coated one by one.

TABLE 6: % DRUG RELEASE FOR BATCHES F009, F010 AND F011

Time (hr)	F009 n=3	F010 n=3	F011 n=3
1	46.2±1.02	47.4±0.32	45.3±1.21
2	58.3±2.05	55.7±1.21	56.8±2.52
4	61.7±2.32	59.8±2.68	61.7±3.20
6	65.3±1.30	64.9±1.32	66.5±0.89
8	70.1±1.39	69.5±3.10	68.6±2.43
10	72.3±2.10	71.9±1.89	72.0±3.09
12	74.0±3.06	73.6±0.29	73.8±2.10
18	82.9±2.09	81.2±2.36	83.7±1.76
24	88.5±2.01	87.4±1.79	87.0±0.97

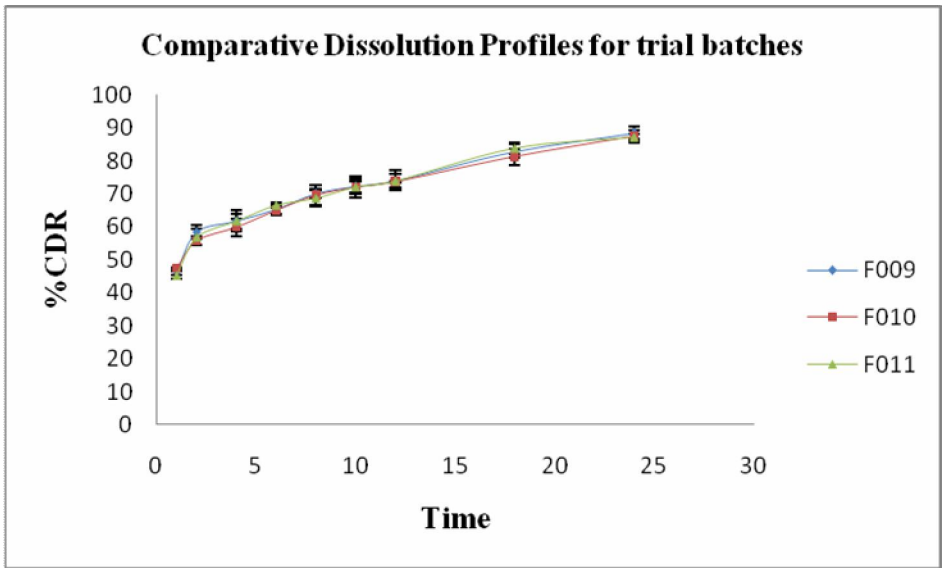

Figure 3
Comparative Dissolution Profiles for Trial batches (F009, F010, and F011).

Now for the trial F009, finally DCP granular form was decided to be taken for the formulation. In this batch, coating formula is increased & batch is prepared. In this batch, some part of the DCP granular form was taken in the extra granular part with aerosol & calcium stearate. 10% granulating solution was used for the wetting of the powder that is drug & DCP granular. Then this blend was transferred to FBC for further granulation. Here the dissolution data obtain was in compliance with required drug release profile.

Trial F010 is for checking the robustness of the formula. Here in place of 10%, 15% of the solution was taken for wetting the mass for higher granulation. Than the blend was transferred to the FBC & remaining was same as F009. Dissolution data obtain was in compliance with required drug release profile. Trial F011 was the final batch as a scale up batch of 10,000 tablets using the formula of F009. The remaining parameters were the same.

SUMMARY

Clomipramine is a tricyclic antidepressant and it is non selective monoamine (norepinephrine and serotonin) reuptake inhibitor. It has extensive 1st pass metabolism and associated with frequent dosing of conventional dosage form makes it a suitable candidate for sustained release dosage form for patient compliance. Preparation of sustained release formulation using hydrophobic polymer eudragit, which is widely used

in industry. So for present work, eudragit having different grades like RL 30D, RS 30D were selected as release retarding agent. The dispersions contain 30% polymer. In present study, once a day sustained release tablet dosage form of clomipramine hydrochloride was prepared using optimized combination of various grades of eudragit. Matrix system of clomipramine hydrochloride based on hydrophobic polymer (eudragit RL 30D, eudragit RS 30D, etc.) was tried individually as well as in combinations. Finally core tablets were coated using HPMC 6 Cps. The batch F011 was prepared according to the formula to fulfill the criteria for the optimized batches and could extend the drug release up to 24 hours. Final optimized batch (F011) obtained were fulfill the criteria for optimized batch and significantly retard the release up to 24 hours with initial loading dose release. So the batch F011 were considered as the optimized batch for once a day sustained release tablet formulation containing clomipramine hydrochloride. Finally, the dissolution profile of the batches F010 & F011 were in compliance with required drug release profile.

CONCLUSION

Present work was directed towards the development and evaluation of sustained release tablet dosage form of clomipramine hydrochloride. Matrix system of clomipramine hydrochloride based on hydrophobic polymer (eudragit RL 30D, eudragit RS 30D, etc.) was tried individually as well as in criteria for optimized batches was defined. For in vitro dissolution the release pattern was selected depending upon dissolution profile in compliance with required drug release profile. Here, initially, bursting effect were needed so initial release in 1st hr was more and for rest of the time period (23 hrs), it was given a sustained release effect.

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