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Research Article

FORMULATION AND EVALUATION OF FILM COATED TICLOPIDINE HYDROCHLORIDE IMMEDIATE RELEASE TABLETS

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ABSTRACT
In the present work attempts were made to with an aim to develop pharmaceutically equivalent, stable, cost effective and quality improved formulation of film coated Ticlopidine Hydrochloride immediate release tablets by direct compression technique. The current study involves preparation and evaluation of Ticlopidine Hydrochloride tablets (250mg), comparison of dissolution rate of optimized formula with innovator's product and estimation of similarity and difference factors. The three superdisintegrents used in the study were Cross carmellose sodium (CCS), Microcrystalline Cellulose (MCC) and Native starch. Six Tablet batches (F1 – F6) having superdisintegrents at different concentrations level were prepared. The prepared batches of tablets were evaluated for uniformity of weight, thickness, hardness, friability, disintegration test and invitro – dissolution study. The formulation F5 containing combination of CCS, MCC and native starch (6, 44.73 & 54.75 mg) showed similar *invitro* disintegration time and drug release as that of marketed product (Tyclid).

Keywords: Ticlopidine Hydrochloride, Superdisintegrents, Immediate release, Tyclid.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration. That is, the drug delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment. Tablet is the most widely used dosage form because of its convenience in terms of self administration, compactness and ease in manufacturing. They are the most widely prepared form of medication both by pharmaceutical manufacturer as well as physicians and patients. They can be mass produced with robust quality controls and other different branding possibilities by means of colored film coating different sizes and shapes for better appearance and improving the patient compliance[1].

Ticlopidine hydrochloride is an inhibitor of platelet aggregation used in the management and prevention of thromboembolic disorders[2]. It is used as adenosine diphosphate [ADP] receptor antagonists in an ant platelet therapy[3]. It is also significantly reduces rest enosis after endovascular therapy in femoropopliteal lesions[4]. It is also effective in the platelet aggregation induced by adrenaline and PAF[5]. It is efficacy in reducing the stroke is similar to that of aspirin[6,7].

Pharmaceutical excipients can be defined as any substance other than the active and is included in the formulation for improving the pharmacokinetic parameters[8]. Diluents, Binders, Disintegrants, Lubricants etc., are the excipients usually added in the formulations of tablets[9]. Native starch, Crospovidone, Crosscarmellose sodium (CCS), Microcrystalline Cellulose (MCC) are some of the superdisintegrants included in the immediate release tablets for better onset of action[9, 10].

MATERIALS AND METHODS

Preformulation studies

Ticlopidine Hydrochloride (API) was evaluated for its, solubility, pH, melting point, loss on drying and hygroscopicity [11,12].

Drug-excipients compatibility studies

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug[11]. Binary mixture of drug with each excipients were prepared and the Samples were tested for physical and chemical changes at 0, 1 & 3 months against control kept at refrigerated condition (2-8˚C, RT & 50˚C)

Formulation of film coated Ticlopidine Hydrochloride immediate release tablets

Direct compression method

After equivalent weight factor calculation, the Ticlopidine Hydrochloride required for the formulation was found to be 284.51 mg. Immediate release tablets were prepared by direct compression method and various formula used in the formulation are shown in table 1. Each formulation having different ratios for superdisintegrents, are mixed uniformly. The prepared powder blend was evaluated for various following parameters. After evaluation of powder blend the tablets were compressed with a rotary punch-tableting machine (Rimek Mini Press- 1) using 11.1 mm normal plain punches [13,14,15].

Coating of tablets [16]

The compressed tablets obtained by direct compression method were coated by pan coating method. The coating formula is given in the table.2.

Physico-mechanical characterization

Density measurement[11]

Different types of density was determined to characterize the API and its flow property

Bulk density

Apparent *bulk* density was determined by placing presieved drug excipients blend into a graduated cylinder and measuring the volume (V_0) and weight (M)

$$\text{Bulk density} = M/V_o$$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed number of taps. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend

was measured.

Tapped density=M/Vt

Flow properties [17]

These differences are reflected in the compressibility index and the hausner'ratio.

It can be calculated by using the following equation

Compressibility index = 100 $(V_0-V_r)/V_0$

Hausner ratio = V_0/V_r

Where, V_0 = bulk volume of the powder

V_r = final tapping volume of the powder

Angle of repose

Angle of repose (ø) was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose was calculated.

$$Ø = \tan\text{-}1(h/r)$$

Evaluation of tablets

All the formulated film coated tablets were evaluated for the following tests and compared with the marketed product (Tyclid).[11]

Weight variation test

Weight variation test was done by weighing 20 tablets individually, by using digital weighing balance Calculating the average weight and comparing the individual tablet weight to the average weight.

Tablet thickness test

The thickness was measured by placing tablet between two arms of the Varnier calipers. 5 tablets were taken and their thickness was measured.

Tablet hardness test

The tablet hardness, which is the force required to break a tablet in a diametr ic compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

Tablet friability test

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_o) or a sample of 20 tablets are dedusted in a dr um for a fixed time (100 r evolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

% Friability = 100 (WO -W) / Wo

In-vitro disintegration time

This test was carried out at 25 ± 2°C in 900 ml of distilled water. Six tablets were taken and one tablet was introduced in each tube, disc was placed and basket rack was positioned in 1 liter beaker containing water 25 ± 2°C and apparatus operated for 3 min with no palable mass and the disintegration time in seconds was noted (Indian pharmacopoeia 2007).

In-vitro dissolution study

Dissolution studies of all tablets were performed using dissolution tester USP II (Paddle type, TDL-08L, Electrolab, India). Tablets were added to the 900 ml of 0.1 N HCl at 37°C ± 0.5°C, which was stirred with a rotating paddle at 75 rpm. At various time intervals of 5, 10, 15 and 30 minutes, 1ml samples was withdrawn and equal volume of fresh medium was replaced in to the dissolution medium after each sampling to maintain its constant volume throughout the test[19]. A Ticlopidine hydrochloride standard stock solution containing 100 µg mL-1 was prepared in a 100 mL volumetric flask by dissolving 10.00 mg of Ticlopidine hydrochloride and then diluted to volume with methanol as diluent. Assay carried out using U.V. spectrophotometer (UV 1700 shimadzu /visible double beam spectrophotometer, Japan) at233nm[7].

RESULTS AND DISCUSSION

Preformulation studies

The results obtained were shown in table 3. The obtained results were complied with the results given in Indian pharmacopoeia. Hence the API selected is a best suit for this formulation.

Drug- Excipient Compatiblity studies

The drug is mixed with each excipients and this binary mixture shows no characteristic change after the specified period of time. This shows the API is compatible with all the ingredients. The results were shown in table 4.

Physico-mechanical characterization

The Bulk density, tapped density, Compressibility index, Hausner ratio and Angle of repose are denoted in the table 5. All the formulation F1-F6 was all within acceptable limits as per USP specification for the above properties. All the above results shows a better selection for the formulation of immediate release tablet.

Tablet evaluation study

The hardness test, thickness test, friability test and weight variation test for all the batches were performed including the marketed drug. All the values for F5 showing a similarity with that of Tyclid. The disintegration time for Tyclid is 635.4±0.067 sec and for F5 it was found to be 630.93±0.12 sec. Results were shown in table 6.

Crosscarmellose sodium, Microcrystalline Cellulose and Native starch at different concentrations are the superdisintegrants employed in each batch. As shown in table, optimum concentration of the superdisintegrants shows better drug release when compared to increase or decrease in its concentrations. Out of six formulations, F6 showed a better drug release (99.95±0.64%) as that of innovator's product (99.76±0.97%) in 30 min. Fig.1

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Table: 1. Formula for Film coated Ticlopidine Hydrochloride immediate release tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Ticlopidine Hydrochloride	284.51	284.51	284.51	284.51	284.51	284.51
Hydrogenated Castor oil	5	5	5	5	5	5
Polyethylene Glycol 6000	5	5	5	5	5	5
Croscarmellose Sodium	5.0	5.5	5.75	6	6.25	7
Microcrystalline Cellulose PH 112	47.23	46.733	46.733	45.733	44.833	44.50
Native starch	53.257	53.257	53.007	53.757	54.904	55.924
Total	**400**	**400**	**400**	**400**	**400**	**400**

Table: 2. Coating formula for Film coated Ticlopidine Hydrochloride immediate release tablets

S.no	Ingredients	Uses	Qty/1000 Tablet (gm)
1.	Hypromellose	Film forming agent	6.60
2.	Lactose monohydrate	Filler	0.69
3.	Titanium dioxide	Opacifier	3.72
4.	Triacetin	Plasticizer	1.38
5.	Iron oxide red	Color	0.03
6.	Purified water	Vehicle	95.00

Table: 3. Preformulation studies on Ticlopidine Hydrochloride

Tests	Observations
Solublity	Practically insoluble in water at neutral pH but freely soluble at pH 1 • Dissolved freely in methanol • Dissolved sparingly in methylene chloride • Practically insoluble in ethyl ether
pH	2.06
Melting point	205°C
Loss on drying	0.21% w/w
Hygroscopicity	Hygroscopic

Table: 4. Compatibility studies of Ticlopidine Hydrochloride with excipients

S.No	Drug+Excipient	Parameter	Initial Value of Parameter	Condition				Comments
				1st MONTH		3rd MONTH		
				50°C	2-8°C	RT	40°C	
1	CLP + Castor oil (Hydrogenated)	Color change	No color change	No color change				Compatible
2	CLP + PEG 6000	Color change	No color change	No color change				Compatible
3	CLP + CCS	Color change	No color change	No color change				Compatible
4	CLP + MCC	Color change	No color change	No color change				Compatible
5	CLP + Native starch	Color change	No color change	No color change				Compatible

Table: 5. Physico-mechanical characterization of Ticlopidine Hydrochloride powder blend

S.No.	Formulation Code	Bulk Density*	Tapped Density*	Compressibility Index (%)*	Hausner's Ratio*	Angle of Repose*
1.	F_1	0.5344±0.012	0.5867±0.01	8.90±0.91	1.09±0.010	26.84±1.26
2.	F_2	0.5377±0.010	0.5888±0.01	8.69±0.25	1.09±0.003	27.63±1.22
3.	F_3	0.5530±0.018	0.6029±0.02	8.28±0.88	1.09±0.010	28.02±1.28
4.	F_4	0.5446±0.016	0.5939±0.02	8.31±0.38	1.09±0.004	26.73±1.26
5.	F_5	0.5452±0.017	0.5964±0.02	8.59±0.37	1.09±0.004	26.61±1.27
6.	F_6	0.5424±0.017	0.5899±0.02	8.04±0.62	1.08±0.007	28.54±1.25

Table: 6. Evaluation of film coated Ticlopidine Hydrochloride immediate release tablets

S.No.	Formulation Code	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Weight variation test (mg)	Disintegration time (sec)
1.	F1	4.5±0.102	4.94±0.008	0.503±0.003	396.83±1.941	149.2±0.06
2.	F2	5.1±0.102	4.895±0.005	0.162±0.002	395.67±1.506	270.7±0.09
3.	F3	5.03±0.33	4.632±0.004	0.232±0.003	403.99±2.24	355.45±0.05
4.	F4	5.6±0.33	4.882±0.006	0.545±0.005	399.45±3.03	567.67±0.05
5.	F5	5.5±0.34	4.952±0.007	0.497±0.009	400.95±1.99	630.93±0.12
6.	F6	5.4±0.32	4.923±0.010	0.658±0.005	399.34±2.01	675.45±0.05
7.	Tyclid	5.5±0.022	4.95±0.005	0.5±0.002	401.65±2.161	635.4±0.067

Mean ± SEM (n=6)

Table: 7. Drug release profile of Ticlopidine Hydrochloride immediate release tablets at 75 RPM in 0.1 N HCl

S.No.	Formulation code	% Drug release			
		5th min	10th min	15th min	30th min
1.	F_1	58.28±0.62	62.61±0.65	78.91±0.96	87.56±0.21
2.	F_2	69.34±0.613	79.59±0.64	84.67±0.64	92.73±0.36
3.	F_3	80.65±0.649	89.59±0.63	91.76±0.54	98.91±0.15
4.	F_4	78.83±0.651	84.68±0.54	90.73±0.48	97.61±0.65
5.	F_5	74.92±0.655	81.98±0.59	90.96±0.19	99.95±0.64
6.	F_6	80.59±0.621	89.31±0.46	91.98±0.56	96.02±0.64
7.	Tyclid	75.60±0.564	80.40±0.59	89.12±0.89	99.76±0.97

Mean ± SEM (n=6)

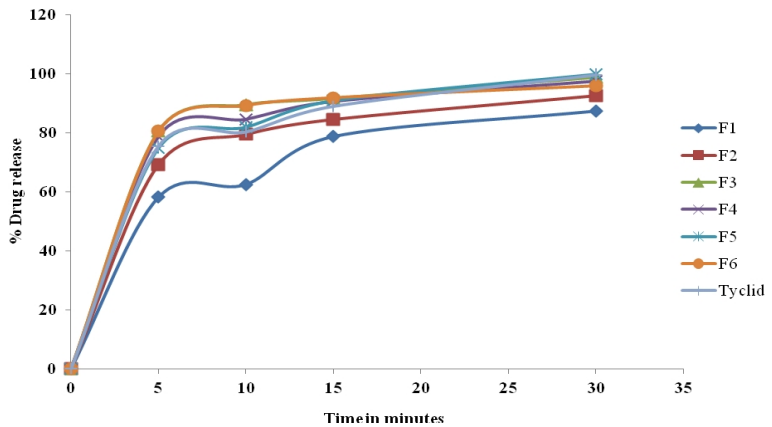

Fig. 1.Drug release profile of Ticlopidine Hydrochloride immediate release tablets at 75 RPM in 0.1 N HCl

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