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FORMULATION AND *IN-VITRO* EVALUATION OF FIXED DOSE COMBINATION OF ESCITALOPRAM AND CLONAZEPAM TABLET

P. Khandelwal, Vikran* and Nirav N.Patel

Mahatma Gandhi College of Pharmaceutical Sciences, Jaipur.ISI-15 (A) RIICO Institutional Area, Sitapura, Tonk Road, Jaipur-302022 (Rajasthan) India.

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***Correspondence for Author**

Vikran

Mahatma Gandhi College of Pharmaceutical Sciences, Jaipur.ISI-15 (A) RIICO Institutional Area, Sitapura, Tonk Road, Jaipur-302022 (Rajasthan) India.

ABSTRACT

An attempt was made to formulate, evaluate the fixed dose combination of Escitalopram-clonazepam tablet. The purpose of such formulation was to synergism the effect of such salts for the treatment of conditions which can used for that particular or with that drug aside. So this method of formulation can also reduce the burden of pills from the patients and risk involve in the side effects. Wet granulation method was employed for the formulation because by direct compression or with dry granulation the disintegration and the binding is not easy to achieve. Beside the active ingrediants of Escitalopram and Clonazepam, tablet contain Maize starch, Lactose, Microcrystalline cellulose, PVPK-30, Aerosil, Croscarmellose sodium, Purified talc and Magnesium stearate. Accelerated stability studies for selected formulation F1 and F3 showed physicochemical stability for a period of one month at 40°C / 75% RH.

Key words: Fixed Dose Combination, Escitalopram, Clonazepam, Wet granulation.

INTRODUCTION

A tablet is pharmaceutical dosage form which is comprises of a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose. The excipients can include diluents, binders of granulating agents, glidants and lubricants to ensure efficient tablet disintigrants to promote tablet break-up in the digestive tract, sweetener or flavor to enhance taste; and pigments to make the tablet visually attractive. The compressed tablet is the most popular dosage form in use today. About two-thirds of all prescriptions are dispensed as solid dosage forms, and half of these are compressed tablets. A tablet can be formulated to deliver an accurate dosage to a specific site, it is usually taken

orally, but can be administered sublingually, buccally, rectally or intra vaginally. The tablet is just one of the many forms that an oral drug can take such as syrups, elixirs, suspensions, and emulsions. Medicinal tablets were originally made in the shape of a disk of whatever color their components determined, but are now made in many shapes and colors to help distinguish different medicines.

Tablets can be made in virtually any shape, although requirements of patients and tablet machines mean that most are round, oval or capsule shaped. More unusual shapes have been manufactured but patients find these harder to swallow, and they are more vulnerable to chipping or manufacturing problems.

Advantages of tablet

- They are a unit dosage form and they offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
- Their cost is lowest of all oral dosage forms.
- They are the lightest and most compact of all oral dosage forms.
- They have the best combined properties of chemical, mechanical and microbiological stability of all oral dosage forms.
- They are in general the easiest and cheapest to package and ship of all oral dosage forms.
- Product identification is potentially the simplest and the cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- They may provide the greatest ease of swallowing with the least tendency for the “hang-up” above the stomach, especially when coated, provided that tablet disintegration is not excessively rapid.

Disadvantages of tablet

- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low density character.
- Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the gastrointestinal tract, or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate or full drug bioavailability.
- Bitter tasting drugs, drugs with an objectionable odor, or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to

compression, or the tablet may require coating. In such case, the capsules may offer the best and lowest cost approach [1].

The purpose to formulate fixed dose combination (FDC) is to decrease the burden of pills from the patients prospective and making the dosage form more effective from the view of clinical action. When two or more drugs are given together as like fixed dose combination, they may either be indifference to each other or produce synergetic or antagonistic. When the action of one drug is increased by another drug given concomitantly, it is said to be synergetic and when one drug inhibit or decreases the action of another said to be antagonistic. The synergistic actions produced by the fixed dose combination drug many remains beneficial for the treatment.

In such condition, FDC can decrease the complexity of dosage regimen, cost of therapy, incidence of ADR and increase the compliance of therapy. Thus decreases the resistance to the treatment. The basic aim of any therapy is to treat a particular aliment with effective and safe drugs. This can be done with either one drug or a combination of drugs. Hence formulations can be classified as single dose formulations and fixed dose combinations. Single dose formulations contain only a single drug with or without additives while fixed dose combinations contain two or more drugs in fixed ratio to each other in a single dosage form.

Advantages of FDC drugs

- The active ingredients used therein are not expected to interact adversely with each other.
- Simpler dosage schedule improves compliance and therefore improves treatment outcomes.
- Reduces inadvertent medication errors.
- Eliminates drug shortages by simplifying drug storage and handling, and thus lowers risk of being “out of stock”.
- Only 1 expiry date simplifies dosing (single products may have different expiry dates).
- Procurement, management and handling of drugs are simplified.

Disadvantages of FDC drugs

- Different pharmacokinetic properties can pose difficulty in frequency of administration and
- in case of development of an ADR.

- The greater are the number of ingredients, the less likely the prescriber or the physician is to know what FDCs are and what their adverse reactions are. A combination makes it more difficult to pinpoint the offending agent responsible for the adverse reaction.
- It is difficult to withdraw the suspected drug alone.
- Dose of one ingredient cannot be altered.

Use of formulated tablet

Escitalopram and Clonazepam combination is indicated for the treatment of a wide variety of mental disorders.

- Enhance the polysynaptic inhibitory processes at all level of the central nervous system(Marshall et al ., 1987).
- Reducing symptoms of generalized social anxiety disorder (GSAD) (Knijnik et al ., 2012).
- Used for the treatment of major depressive disorder(Burke , 2002).
- Suppresses GABA,-Mediated Inhibition in thalamic relay neurons through effects in nucleus reticularis (Huguenard, 1994).
- Inhibit the reuptake of serotonin (5-HT) by the pre-synaptic neuron, thus maintaining higher level of 5-HT in the synapse (Kannuri et al .,2007)

MATERIAL AND METHODS

Escitalpram was obtained from M/S Nishchem International, Mumbai, India and Clonazepam from Pharma Force Lab, Paonta Sahib, Himachal Pradesh and Microcrystalline Cellulose PH-102 from Suren Healthcare, Ahmadabad andLactose from Mars Healthcare Pvt. Ltd, New Delhi and Maize starch obtained from Clarion Pharmaceutical Co., New Delhi and PVPK-30 from Nishchem International, Mumbai, India.All other chemicals were used as received(Table.1).

Preformulation studies

Drug-excipients compatibility

Fourier Transform Infra Red spectroscopy

Fourier Transform Infra Red (FTIR) spectra of pure drugs with or without excipients were measured FTIR spectrophotometer. The spectra were recorded within 4000-400 cm-1 wave numbers.

Preparation of tablets

Escitalopram-clonazepam tablets were prepared by using wet granulation technique. The active ingredients, lactose, maize starch and MCC were weighed and passed (sieve) through mesh no.60. Premixing the ingredients for 10 min. Aerosil, croscarmellose sodium,magnesium stearate and purified talc were also passed through mesh no.40.Then prepared the binding solution (PVPK-30 +water).Mixed the binding solution in pre mixed blend. Drying the wet granule in fluid bed dryer. Sifting and milling the dry granules through 20 mesh stainless steel sieve & 1.5mm SS screen and mixed of the granules for 40 min. Addition of the magnesium state, aerosol, croscarmellose sodium and purified talc (passed through 60 mesh) and blend for 5 minutes and compressed the tablets.

Table 1 Composition of Escitalopram-clonazepam tablets(F1 to F5)

S. No.	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)
1	Escitalopram	13.42	13.42	13.42	13.42	13.42
2	Clonazepam	0.535	0.535	0.535	0.535	0.535
3	Microcrystalline Cellulose	42.00	41.00	40.00	41.00	43.00
4	Lactose	55.80	56.80	57.80	55.80	55.80
5	Maize Starch	12.30	13.30	13.30	13.00	12.30
6	PVPK-30	1.90	1.90	1.90	2.20	1.90
7	Aerosil	4.00	3.00	3.00	5.00	3.00
8	Croscarmillose Sodium	3.00	3.00	3.00	2.00	4.00
9	Purified Talc	4.00	4.00	4.00	4.00	4.00
10	Magnesium Stearate	3.00	3.00	3.00	3.00	3.00
	Total Weight	140.000	140.000	140.000	140.000	140.000

Evaluation of Blend Granules

Angle of Repose

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method. The granules mass was allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This forms a pile of angle of granules

on the paper. The angle of repose was calculated by substituting the values of the base radius 'R' and pile height 'H' in the following equation

$$\tan \theta = h/r$$

Hence, $\theta = \tan^{-1} h/r$

Where, θ = Angle of repose

h = Height of the cone

r = Radius of the cone base

Flow Rate

Flow rate of a powder has been defined as the rate at which the particular mass emerges through the orifice of funnel of a suitable diameter. The flow rate for granules of each formulation was determined by pouring accurately weighed quantities of granules in funnel with an orifice of 8 mm diameter. The time required for the complete granule mass to emerge out of the orifice was recorded using a stopwatch. The flow rate was calculated from following equation

$$\text{Flow Rate} = \frac{\text{Weight of granules}}{\text{Time in seconds}}$$

Bulk Density & Tapped Density

Both loose bulk density (BD) and tapped bulk density (TD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml 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. BD and TD were calculated using the following formulas

BD = Weight of the powder/ Volume of the packing

TD = Weight of the powder/ Tapped volume of the packing.

Carr's Compressibility Index

An indirect method of measuring powder flow from bulk densities was developed by Carr. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated according to equation[7] given below

$$\% \text{ Compressibility} = \frac{BD - TD}{BD} \times 100$$

Where,

BD = Bulk density

TD = Tapped density

Evaluation of Tablets

Tablet Thickness

Thickness and of tablets are important for uniformity of tablet size. Thickness was measured using digital VernierCalipers. Five tablets from each batch were used, and average value was calculated.

Tablet Hardness

The resistance of tablets to shipping or breakage, under conditions of storage, transportation and handling before usage depends on its hardness. For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester (Cadmach). The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2. Generally, a minimum of 4 kg/cm^2 hardness is considered acceptable for uncoated tablets.

Friability

Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. For each formulation, the friability tablets were determined using the Roche Friabilator (Lab Hosp.). This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. In this approximately 6 gm (w_0) of the dedusted tablets are subjected to 100 free falls in a rotating drum and are than reweighed (w). Percent friability (% F) was calculated as follows (Lachman et al., 1987),

$$\% \text{ Friability} = \frac{\text{Initial weight}(w0) - \text{Final weight}(w)}{\text{Initial weight}} \times 100$$

A loss of less than 1 % in weight in generally considered acceptable.

***In vitro* disintegration test**

A generally accepted maxim is that for a drug to be readily available to the body, it must be in the solution. For most tablets, the first important step toward solution is the breakdown of the tablet in to smaller particles or granules, a process known as disintegration. The time that it takes a tablet to disintegrate is known as disintegration time.

Average Disintegration time for each formulation was determined by USP Disintegration apparatus. Six tablets from each formulation were evaluated for the DT and average DT was found out.

Stability studies

Stability study was carried out on optimized formula. The tablets were stored at 40±2°C/75±5% RH for one month. then the samples were evaluated for various physical tests (Corveleyn et al., 1997).

RESULT AND DISCUSSION

Drug-excipient compatibility study

FT-IR spectroscopy study was carried out separately to find out, the compatibility between the drugs (Escitalopram oxalate and Clonazepam) and Croscarmellose sodium, Lactose, Maize starch and microcrystalline cellulose used for the preparation of tablets. The FT-IR was performed for drug and the physical mixture of drug-excipients(Fig.1 and Fig.2).

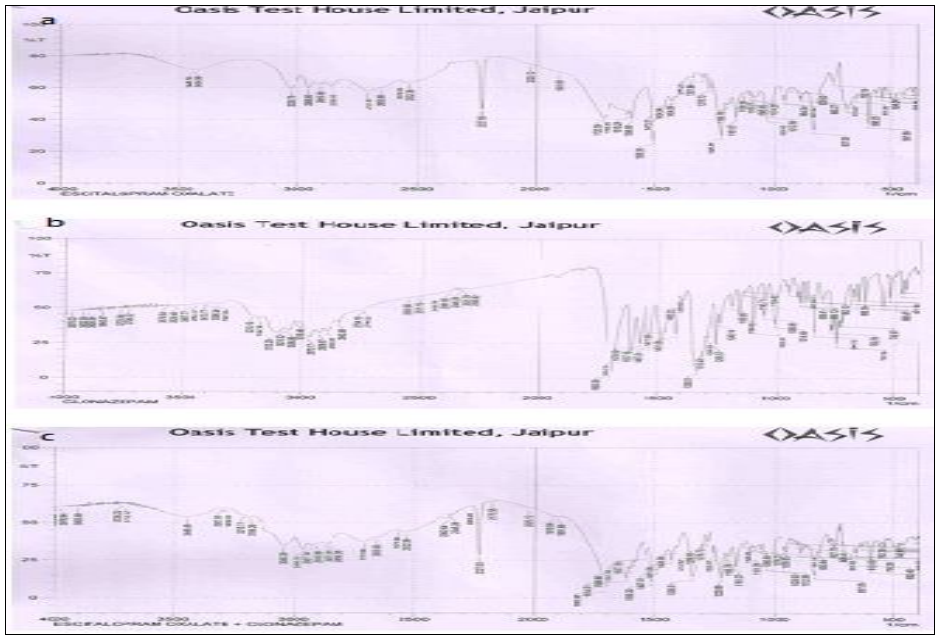

Fig. 1 FTIR spectra of (a)Escitalopram oxalate , (b)Clonazepam, (c)Escitalopram oxalate+ clonazepam.

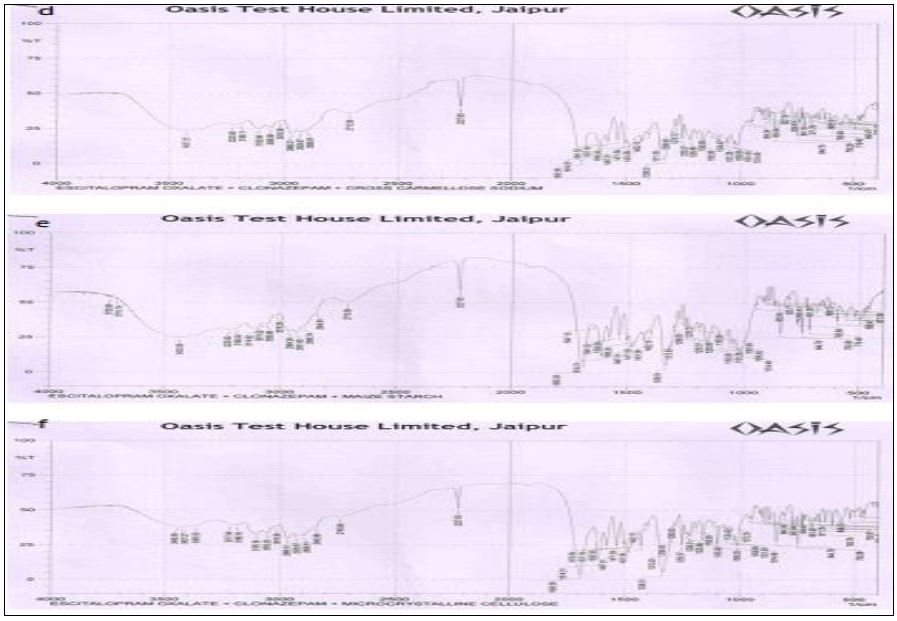

Fig. 2 FTIR spectra of Escitalopram oxalate+ Clonazepam with (d) croscarmellose sodium, (e) maize starch,(f) microcrystalline cellulose.

Evaluation of Blend granules

Angle of Repose

Angle of repose was determined generally by fixed funnel method. Granules of all the batches showed average angle of repose from 26.37^{o}. Angle of repose gives a qualitative assessment of the internal cohesive and frictional effects under low levels of external loading, as might apply in powder mixing, or in tablet die or capsule shell filling operations. Angle of repose method, is also called Dynamic angle, and preferred, since they closely mimic the manufacturing situation, in which the powder is in motion. Values of angle of repose are rarely less than 20°, and values of up to 40° indicates reasonable flow potential (Table 2).

Table 2 Angle of repose of blend granules

Formulations	Height (h) Cm	Radius (r) Cm	tanθ= h/r	θ = tan-1 h/r	θ Avg
F_1	2.2	4.0	0.555	25.96	
F_2	2.0	3.9	0.512	27.11	26.37^{o}
F_3	2.1	4.2	0.555	27.14	
F_4	2.0	4.1	0.487	27.64	
F_5	2.1	4.4	0.477	25.50	

Bulk Density & Tapped Density

The values of Bulk Density and Tapped Density for all formulations were found to be in the range from 0.440 to 0.447 and 0.507 to 0.525 respectively (Table 3 and 4).

Table 3 Bulk density of blend granules

Formulations	Weight of the powder (g)	Bulk volume (c.c)	Bulk density = wt/volume(gm/c.c)	Weight of the powder (g)	Average
F_1	15.225	35	0.435	15.225	
F_2	15.120	35	0.440	15.120	0.444
F_3	15.120	34	0.444	15.120	
F_4	15.229	34	0.447	15.229	
F_5	15.216	35	0.434	15.216	

Table 4 Tapped density of blend granules

Formulations	Weight of the powder (g)	Tapped volume(c.c)	Tapped density = wt/volume (gm/c.c)	Weight of the powder (g)	Average
F_1	15.225	29	0.525	15.225	
F_2	15.120	30	0.513	15.120	0.514
F_3	15.120	29	0.521	15.120	
F_4	15.229	30	0.507	15.229	
F_5	15.216	30	0.507	15.216	

Flow Rate

Flow rate ranges from 0.99 to 1.23 gm/min. Flow rate of a powder has been defined as the rate at which the particular mass emerges through the orifice of funnel of a suitable diameter(Table 5).

Carr's Compressibility Index

Values of Carr's index lies between 11.83 to 17.14 . Values of Carr's index below 15 % usually show good flow characteristics, but readings above 25 % indicate poor flowability(Table 5).

Table 5 Compressibility index and flow rate of blend granules

Formulations	Compressibility Index	Flow Rate (gm/min)
F_1	17.14	1.10
F_2	14.23	1.08
F_3	14.77	1.23
F_4	11.83	0.99
F_5	14.39	1.14

Evaluation of Tablets

General Appearance

Table 6 Appearance of tablets of each formulation

Formulation	Colour	Odour	Taste	Shape	Identification marks
F1	White	odourless	Slightly bitter	Round shaped	Tablets both side plain.
F2	White	odourless	Slightly bitter	Round shaped	Tablets both side plain.
F3	White	odourless	Slightly bitter	Round shaped	Tablets both side plain.
F4	White	odourless	Slightly bitter	Round shaped	Tablets both side plain.
F5	White	odourless	Slightly bitter	Round shaped	Tablets both side plain.

Tablet Thickness

Thickness of the tablets of the formulations F_1 to F_5 varied from 3.10 to 3.28 mm (Table.7).

Tablet Hardness

Hardness of tablets of each formulation was measured and found in the range of 37 to 42N (Table.7).

Table 7 Thickness and hardness of tablets of each formulation

Formulations	Thickness (mm)	Hardness (N)
F_1	3.15-3.25	38
F_2	3.10-3.23	37
F_3	3.15-3.27	40
F_4	3.18-3.25	39
F_5	3.12-3.28	42

Friability

Percentage weight loss of the tablets of each formulation was measured and shown in table 8.and found to be in the range of 0.5 to 0.7%.The percentage friability for all the formulations was below 1% indicating that the friability is within the prescribed limits (Table.8).

Table 8 Friability of tablets of each formulation

Weight of Tablets	F1	F2	F3	F4	F5
Initial weight	1405mg	1406mg	1404mg	1405mg	1407mg
Final weight	1397mg	1395mg	1394mg	1496mg	1397mg
% friability	0.5%	0.7%	0.7%	0.6%	0.7%

Disintegration test

Disintegration time for each batch was found to be in the range of 4min 25 sec to 9 min 30 sec (Table.9).

Table 9 Disintegration time of tablets of each formulation

Formulation Parameter	F1	F2	F3	F4	F5
Disintegration Time	8min 40 sec	4min 25 sec	7 min 45 sec	9 min 30 sec	5min 10 sec

In-vitro disintegration time Escitalopram-clonazepam tablet was found to be in the range of 4 -10 min. the disintegration time of all formulations was less than 10min. Disintegration test of Escitalopram-clonazepam tablets was in limit.

Stability studies

Stability study was conducted for all formulations according to procedure described in the methodology. The stability studies was carried out on selected formulation F1 stored at 40° C / 75% RH for one month as these formulation provided desired results. There was no significant taste, color and odor changes at 40° C / 75% RH temperature. There was no significant variation in the disintegration time, and degradation profiles (evaluate by HPLC) after one month of stability studies (Table.10).

Table 10 Detected formulation F1 stored for stability studies at 40°c / 75%RH

Formulation code	Hardness (Newton)	Disintegration time (min.)	Friability in %
F1	38	8min 45sec	0.5

HPLC determination for stability study

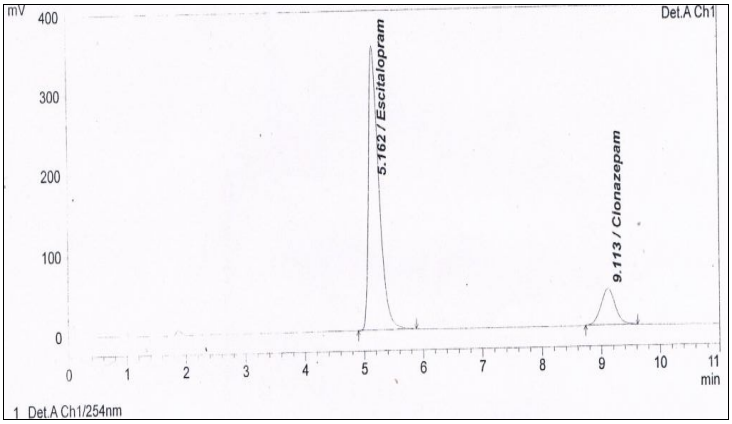

Fig. 3 HPLC spectra of Escitalopram oxalate-Clonazepam of F1

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