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FORMULATION DEVELOPMENT AND INVITRO EVALUATION OF MOUTH DISSOLVING TABLETS OF PAROXETINE HCL BY DIRECT COMPRESSION METHOD

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ABSTRACT

The present study is formulation and evaluation of immediate release tablets of Paroxetine. HCl with respect to Direct compression method used for formulating tablets was best suitable to achieve 100% results. Preformulation studies involving organo-leptic bulk density, angle of repose, tapped density, compressibility index, hausner ratio, melting point range, pH and solubility were carried out as per USP specifications. Drug excipients compatibilities were carried out physical, which showed no significant change in any way to the mixture. Polymers such as Polyplasdone (Crospovidon-XL), Croscarmellose Sodium (CCS), Sodium Starch Glycolate (SSG) were utilized in the trails. All the physical evaluations carried in Preformulation studies were carried out on all the three different polymers utilized. All the formulations exhibited values within the acceptable range. Tablets were evaluated for weight variations, hardness, friability, thickness and Dissolution studies. Release studies were carried out in 7.4 pH Saline, for 20 minutes. Evaluated samples for all the three polymer systems. Results indicated that formulation F_{12}, gave 98.14% release within 8 minutes which is formulated with Crospovidon-XL alone. Assay was carried out for formulation F_{12} and was found to be 96.12%. Remaining formulations gave fluctuating release profiles. The formulation F_{12} was considered to be better among the trails accomplished.

KEYWORDS: Paroxetine, Preformulation, Polymers, Immediate release tablets, Dissolution rate.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reason that the oral route achieved such popularity may be attributed to its ease of administration as well as the traditional belief that by oral administration the drug is well absorbed as the food staffs ingested daily. In fact the development of pharmaceutical products for oral delivery, irrespective of physical form involves varying extents of optimization of dosage form within the inherent constraints of GI physiology. Therefore a fundamental understanding of various disciplines, including GI physiology Pharmacokinetics, pharmacodynamics and formulation design are essential to achieve a systemic approach to the successful developmentof an oral dosage form. The more sophisticated a delivery system the greater is the complexity of these various disciplines involved in the design and optimization of the system. In any case the scientific development of oral drug delivery system consists of a basic understanding of the following there aspects.[1]

a) Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug.
b) The anatomic and physiologic characteristic of the GIT.
c) Physicochemical characteristic and the drug delivery modeof the dosage form to be designed.

Significance of mouth dissolving tablets

- They provide good stability, accurate dosing, easy manufacturing small packaging size and easy to handle by patients.
- No risk of obstruction of dosage from, which is beneficial for travelling patients who do not have access to water.
- Easy to administer for pediatric, geriatric and institutionalized patients. (especially for mentally retarded and psychiatric patients)
- Rapid disintegration of the tablet results in quick dissolution and rapid absorption which provide rapid onset of action.
- Medications as “bitter pill” has changed by excellent mouth feel property produced by the use of flavors and sweeteners in mouth dissolving tablets.
- Bioavailability of drugs that are absorbed from mouth, pharynx and oesophagus is increased.
- Pregastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability.

- Improved taste and not produce any residue in the mouth.
- Insensitive to environmental conditions.

Paroxetine is a selective serotonin reuptake inhibitor (SSRI) used in the therapy of depression, anxiety disorders and obsessive-compulsive disorder. Paroxetine therapy can be associated with transient asymptomatic elevations in serum aminotransferase levels and has been linked to rare instances of clinically apparent acute liver injury it is Chemically called as (3S,4R)-3-(1,3-benzodioxol-5-yloxymethyl)-4-(4-fluorophenyl)piperidine.[2]

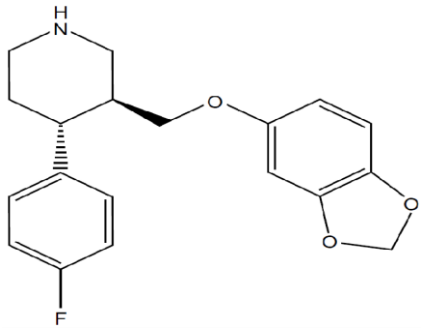

Figure 1: Chemical structure of paroxetine HCl.

EXPERIMENTAL WORK[3-6]

MATERIALS AND METHODS

Paroxetine HCL collected from Apex Pharmaceuticals, MCC PH 102 (Avicel 102), Polyplasdone XL (Crospovidone XL-10), Croscarmellose sodium (CCS), Sodium Starch Glycolate (SSG), Magnesium stearate, Mannitol SD-200, Aspartame purchased from Loba chem Ltd. Hyderabad.

Methodology

Preformulation

Organoleptic properties

Color and Nature

Taste and odour

Particle Size, Shape and Surface Area

Physical characteristics

Flow properties

Angle of repose

Bulk density

Angel of repose	Flowability
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Measurement of powder compressibility

The compressibility Index are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free flowing powder, such interactions are generally less and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between bulk and tapped densities will be observed. These differences are reflected in the compressibility Index Calculated by the formula,

$$\text{\% Compressibility (Carr's index)} = \frac{\text{Tapped density - Initial bulk density}}{\text{Tapped density}} \times 100$$

Melting point

Solution properties

pH of the solution

Solubility

Identification of drug and compatibility study

Identification of drug By FT-IR

UV Spectroscopic method for analysis of paroxetine

Calibration curve of paroxetine

Measured the absorbance of the above prepared standard solutions by using phosphate saline buffer (PBS 7.4) at max 235 nm. Plotted a graph of concentration (in g/ml) on X axis and absorbance (in nm) on Y axis

Formulation and Development of paroxetine hcl immediate release tablets

Ingredients (in mg)	Formulation batches											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Paroxetine hcl	50	50	50	50	50	50	50	50	50	50	50	50
Mcc ph 102 (avicel 102)	200	200	200	200	200	200	200	200	200	200	200	200
Polyplasdone xl (crospovidone xl-10)									4	8	12	16
Croscarmellose sodium (ccs)	4	8	12	16								
Sodium starch glycolate (ssg)					4	8	12	16				
Mannitol	87	83	79	75	87	83	79	75	87	83	79	75
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Aspartamate	7	7	7	7	7	7	7	7	7	7	7	7
Average weight	350	350	350	350	350	350	350	350	350	350	350	350

EVALUATION[7-13]

PRE-COMPRESSION PARAMETERS

Angle of repose

Determination of bulk density and tapped density

Measurement of Hausner ratio and Carr's Index

Weight variation test

Friability test:

Hardness test

Monsanto Hardness Tester

Pfizer Tablet Hardness Tester

Thickness Test

Diameter and Shape

Drug content

Weigh and powdered 10 tablets in a mortar. From this powder equivalent to 100mg of Paroxetine was taken in a 100ml volumetric flask to this water was added and then the solution was subjected to sonication for about 10min's for complete solubilization of drug and the solution was made up to the mark with water filtered the drug content was estimated by measuring the absorbance at 244 nm by using UV- Visible spectrophotometer.

Disintegration time

The test is performed *invitro* to determine the time in which a tablet disintegrates in the water at the 37±2°C. The apparatus which is used to simulate all the conditions of mouth, for the determination of disintegration time is called as Disintegration Time. It consist of two hot plates with housing for beakers, thermostatically controlled heaters to maintain the temperature, two baskets each having provision for fixing 6 glass or plastic tubes provided with guided discs and stainless wire mesh. Each unit is suitable for performing two tests at a time. The glass or plastic tubes are open at one end and fitted with sieve No. 10 mesh at the other end. The tubes are suspended in bath containing water or suitable liquid which is maintained through a distance of 75mm, the volume of the liquid and the distance of movement is adjusted in such a way that the highest point, the sieve should break the surface of the liquid.

Six tablets are placed in each of the six tubes along with a guided plastic disc over the tablets tube and the assembly was suspended into the 1000ml beaker containing Water maintained at 37±2°C and operated the apparatus for 15 minutes. The tubes are allowed to move up and down as per the specification discussed above and the disintegration time is noted when all the tablets particles have passed through the sieve. The disintegration time should comply with official time unless otherwise in the monographs. The assembly was removed from the liquid and the tablets were observed. If one or two tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not less than 16 of the total of 18 tablets tested are disintegrated.

Wetting time and water absorption ratio

Dissolution Apparatus of Immediate Release Paroxetine tablets

invitro dissolution of Paroxetine was studied in USP dissolution apparatus (Electrolab) employing a Basket stirrer. 900 ml Water phosphate saline buffer (PBS 7.4) was used as dissolution medium at 50 rpm. The temperature of 37 ± 0.5 °C was maintained throughout the experiment. Complex equivalent to mg of Paroxetine was used in each test. 5 ml of sample of dissolution medium were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 235 nm after suitable dilution with phosphate buffer. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. The amount of Paroxetine released was calculated and plotted against time and compared with marketed drug was studied.

***In-vitro* release profile**

Medium: phosphate saline buffer (PBS 7.4).

Apparatus: USP II (Paddle)

Speed: 50 rpm

Time: 45 minutes

Temperature: 37 ^{0}C ± 0.5 ^{0}C

λ Max: 235 nm

Perform the test on six tablets place one tablet in each dissolution vessel containing 900 ml of phosphate saline buffer (PBS 7.4) maintained at 37 0C ± 0.5 0C. At specified time withdrawn required amount of sample and replace the same amount with (maintain sink condition), then absorbance was taken and calculate percentage release.

$$\% \text{ Purity} = \frac{\text{Absorbance X 900 X Dilution}}{\text{Slope X 1000 X label claim}} \times 100$$

RESULTS AND DISCUSSION

Pre formulation studies

Organoleptic properties

These tests were performed as per procedure. The results are illustrated in following table.

Table 1: Organoleptic properties.

Test	Specification / limits	Observations
Color	White color Crystalline	white powder
Odour	Odourless	Odourless

Angle of repose

Table 2: Angle of repose.

Material	Angle of repose
Paroxetine	34o.36”

Bulk density and tapped density

Table 3: Bulk Density and Tapped density.

Material	Bulk Density (gm/ml)	Tapped density (gm/ml)
Paroxetine	0.45	0.51

Powder compressibility

Table 4: Powder compressibility.

Materials	Compressibility index	Hausner ratio
Paroxetine	32.41%	1.44

Solution properties

pH of the solutions

Table 5: pH of the solutions.

Material	Test	Specification	Observation
Paroxetine	pH	5.3	Complies

Solubility

Table 6: Solubility.

Test	Specification	Result
Solubility	It is soluble in water and slightly soluble in isopropyl alcohol.	Complies

Precompression parameters

Evaluations of powder

Table 7: Evaluations of Powder.

Batch . N0.	Angle of Repose(0)	Bulk Density (g/ ml)	Tapped bulk density (g/ml)	Carr’s index (%)	Hausner’s Ratio
F1	27°46'	0.453	0.512	11.40	1.24
F2	26°27'	0.489	0.532	11.81	1.26
F3	27°32'	0.412	0.554	13.63	1.21
F4	24°17'	0.409	0.512	14.96	1.26
F5	24°.52'	0.467	0.568	12.13	1.19
F6	24°.26'	0.449	0.587	11.12	1.11
F7	25°.33'	0.456	0.501	11.33	1.23
F8	27°.68'	0.467	0.569	12.28	1.22
F9	23°.91'	0.471	0.547	13.88	1.17
F10	23°.28'	0.413	0.534	12.52	1.24
F11	26°.11'	0.464	0.561	11.14	1.23
F12	26°.58'	0.491	0.545	12.39	1.26

Evaluation of paroxetine tablets

Table 8: Evaluation of Paroxetine Tablets.

Batch. No	Weight Variation (%)	Friability (%)	Thickness (mm)	Hardness (Kg/cm2)	Wetting Time (Sec)	DISINTEGRATION TIME (seconds)
F1	350±1.52	0.41	2.12±0.2	2.13	130	135
F2	350±2.37	0.34	2.02±0.2	2.61	104	108
F3	348±1.44	0.30	2.23±0.1	2.12	76	80
F4	351±1.86	0.48	2.12±0.1	2.34	63	66
F5	351±2.56	0.48	2.23±0.1	2.62	118	122
F6	351±2.13	0.48	2.10±0.1	2.78	81	84
F7	350±1.52	0.39	2.05±0.2	2.51	53	56

F8	351±1.49	0.40	2.08±0.3	2.59	45	48
F9	351±2.37	0.39	2.22±0.2	2.54	104	107
F10	350±1.91	0.51	2.16±0.1	2.38	65	69
F11	350±1.34	0.46	2.09±0.2	2.42	45	51
F12	351±2.03	0.59	2.23±0.2	2.53	18	21

The weight variation of the tablet in the range of ± 1.44% to ± 2.56% (below 5%) complying with pharmacopeial specification.

The friability of the tablet in the range of 0.23 % to 0.59% (below 1%) complying with pharmacopeial specifications. The thickness of the formulations from F_1- F_{12} was found to be in the range of 2.02±0.2 to 2.23±0.2 and hardness of the formulated tablets was found to 2.13 to 2.78 indicating a satisfactory mechanical strength.

The Wetting time of the formulations from F_1- F_{12} was found to be in the range of 18-130 seconds. Lower wetting time implies a quicker disintegration of the tablet. F_{12} shows very lower wetting time it reflects in faster DT.

Water absorption ration is around 67% shows for the formulation F_{12}

Cumulative % Release of Paroxetine Mouth Dissolving Tablets F_1-F_{12}

Table 9: Cumulative % Release of Paroxetine Mouth Dissolving Tablets F_1-F_{12}.

Time (min)	% Drug Release of Formulations											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	24.21	28.21	31.47	34.71	15.62	21.23	24.02	29.63	22.13	30.12	34.23	40.41
2	40.39	46.45	50.39	54.07	29.65	30.43	35.31	38.21	38.39	46.43	51.17	56.43
4	53.91	59.62	61.22	64.73	42.32	42.86	43.17	45.73	53.12	64.64	69.17	76.73
6	66.26	68.71	71.46	78.38	54.43	56.33	58.45	61.72	69.46	77.31	82.45	89.27
8	75.54	76.63	81.92	86.42	67.09	68.90	70.51	72.08	82.31	89.37	90.90	98.14
10	89.19	85.22	89.75	92.53	75.34	76.58	79.14	85.74	97.18	99.33	98.92	---
12	93.65	91.38	93.71	97.34	81.26	87.10	89.91	97.19	97.25	---	---	---
15	96.78	98.76	99.27	99.81	91.47	94.39	96.24	99.74	---	---	---	---
17	98.37	---	---	---	97.38	98.12	98.69	---	---	---	---	---

From the *invitro* dissolution study of all formulations (F1-F12), formulation F12 release around 98% of drug at the end of 8 min's for an immediate release tablets of Paroxetine. Therefore, the F_{12} formulation chosen as the best formulation from all 12 batches.

SUMMARY AND CONCLUSION

The present study involves formulation and evaluation of immediate release tablets of Paroxetine HCl with respect to Direct compression method used for formulating tablets was best suitable to achieve 100% results. Preformulation studies involving organoleptic bulk density, angle of repose, tapped density, compressibility index, Hausner ratio, melting point range, pH and solubility were carried out as per USP specifications. Drug excipients compatibilities were carried out physical, which showed no significant change in any way to the mixture Polymers such as Polyplasdone (Crospovidon-XL), Croscarmellose Sodium (CCS), Sodium Starch Glycolate (SSG) were utilized in the trails. All the physical evaluations carried in preformulation studies were carried out on all the three different polymers utilized. All the formulations exhibited values within the acceptable range. Tablets were evaluated for weight variations, hardness, friability, thickness and Dissolution studies. Release studies were carried out in 7.4 pH Saline, for 20 minutes. Evaluated samples for all the three polymer systems. Results indicated that formulation F12, gave 98.14% release within 8 minutes which is formulated with Crospovidon-XL alone. Assay was carried out for formulation F_{12} and was found to be 96.12%. Remaining formulations gave fluctuating release profiles. The formulation F_{12} was considered to be better among the trails accomplished.

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