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RESEARCH ARTICLE

Formulation and *In-Vitro* Evaluation of Oro Dispersible Tablets of Atovaquone Solid Dispersion

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ABSTRACT

Atovaquone is a chemical compound that belongs to the class of naphthoquinones. Atovaquone is a hydroxy-1,4-naphthoquinone, an analog of ubiquinone, with antipneumocystic activity. The main objective of the present work was to improve the solubility and dissolution rate of poorly water soluble anti-hypertensive drug Atovaquone by Solid dispersion technology using hydrophilic polymer poloxamer 407 as carrier. Nine formulations were prepared by employing primellose ,explosol and crospopharm as super disintegrants. The prepared formulations were evaluated and characterized. All the results of pre-compression parameters were found to be satisfactory and post-compression parameters showed good mechanical strength and good uniformity in all formulations. Based on the in-vitro dissolution studies F3 formulation was considered as the optimized formulation since it has shown the maximum drug release of 97.21% in 60mins compared to all other formulations.

Keywords: Atovaquone, Primellose, Explosol and Crospopharm, solid dispersion.

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CONTENTS

1. Introduction

Solid dispersion is containing at least two different components one is hydrophilic matrix and another is hydrophobic drug, the matrix may be either amorphous or crystalline, the drug can be dispersed either amorphous or crystalline particles .Solid dispersion systems illustrated in literature to enhance the dissolution properties of poorly water soluble drugs. Such as solubilization of drugs in solvents, salt formation, complex forms with cyclodextrin and sometimes particle size reduction also utilized to improve the dissolution of poorly water soluble drugs. On other hand solid dispersion system offers variety of formulations by using excipients to enhance dissolution of poorly water soluble drugs for oral administration.

2. Materials and Methods

Materials: Atovaquone, Microcrystalline cellulose, Explosol, Primellose, Crospopharm, Magnesium stearate, Talcall the chemicals were laboratory grade.

Formulation of Oral dispersible tablets of Atovaquone:

Preparation of Solid Dispersions of Atovaquone were prepared using Poloxamer 407 as a carrier by different methods like Kneading method and different drug to poloxamer ratios i.e., 1:1, 1:2 and 1:3.Atovaquone was dissolved in ethanol and to this solution Poloxamer 407 was added. Then the mixture was triturated in a glass mortar until it forms paste like consistency and allowed to drug. The dried powder was passed through sieve no: 60 and the final product was stored in a desiccator until use.Oral dispersible tablets of Atovaquone were prepared by direct compression method. The physical mixtures and solid dispersions equivalent to dose of drug Atovaquone were taken. They are uniformly mixed with directly compressible diluents (MCC), lubricant (Magnesium stearate) and super disintegrants (Explosol, PrimelloseandCrospopharm) in required quantities as per the formulae.

Evaluation of post compression parameters for prepared Tablets:

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

3. Results and Discussion

Standard Calibration curve of Atovaquone:

It was found that the estimation of Atovaquone by UV spectrophotometric method at λ_{max}276 nm in pH 6.8 Phosphate buffer had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2- 10µg/ml. The regression equation generated was y = 0.660x + 0.003, R^2 = 0.998.

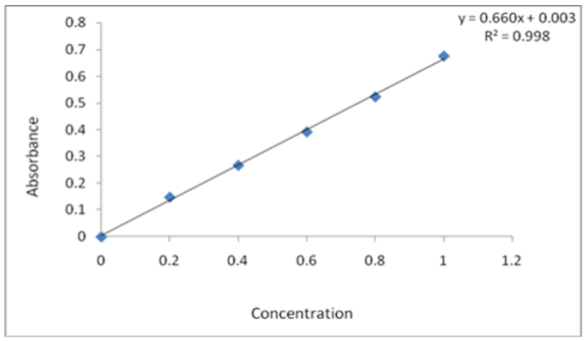

Fig 1: Standard graph of Atovaquone in pH 6.8 Phosphate buffer

Pre-compression parameters:

The data's were shown in Table 3.The values for angle of repose were found in the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.41 to 0.50 (gm/cc) and 0.50 to 0.58 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 14.56% to 18.01%.The Hausner ration fall in range of 1.09 to 1.22. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.'

Post compression Parameters

Weight variation test:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 4. The average weight of the tablet is approximately in range of 498 to 509 mg, so the permissible limit is ±10% (=500mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test:

Hardness of the three tablets of each batch was checked by using Monsanto hardness tester and the data's were shown in Table 4. The results showed that the hardness of the tablets is in range of 2.3 to 2.8 kg/cm^2,which was within IP limits.

Thickness:

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table-4 .The result showed that thickness of the tablet is raging from 3.29 to 3.71.

Friability:

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 4. The average friability of all the formulations lies in the range of 0.41 to 0.51 % which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

In vitro disintegration time:

Tablets of each batch were evaluated for in vitro disintegration timeand the data's were shown in the Table 4. The results showed that the disintegration time of prepared tablets were in the range of 48 to 72 seconds.

Assay:

Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 97.21 -99.54%.

In-vitro Dissolution studies:

In-vitro dissolution studies were carried out by using 500ml of pH 6.8 Phosphate buffer in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 30 min.

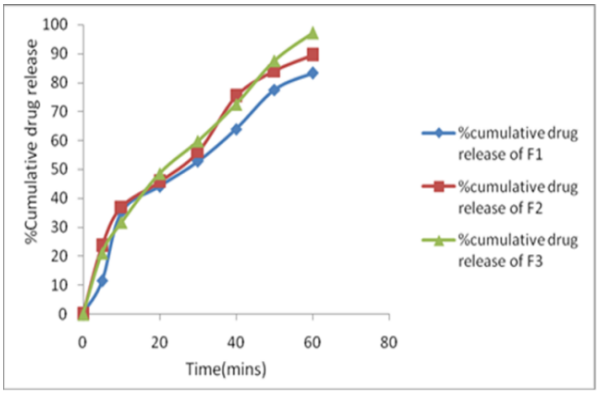

Fig 2: Dissolution profile of formulations prepared with Explosol as super disintegrate

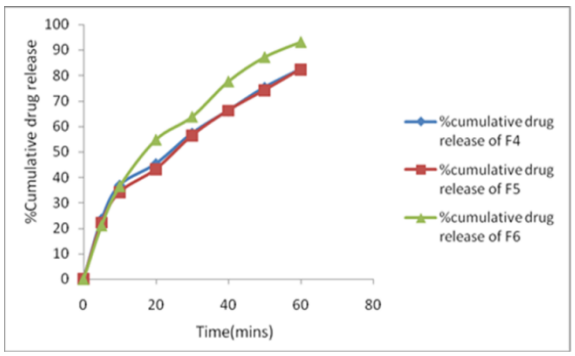

Fig 3: Dissolution profile of formulations prepared with Primellose as super disintegrate

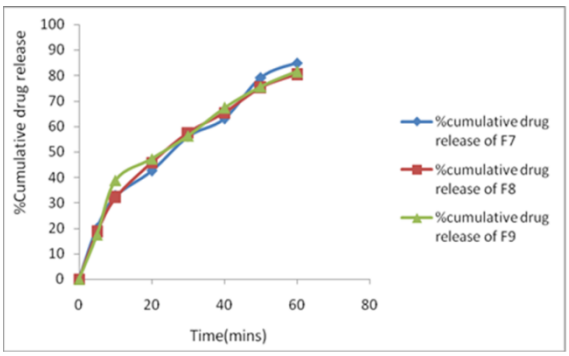

Fig 4: Dissolution profile of formulations prepared with Crospopharm as super disintegrate

Table 1: Composition of various tablet formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Atovaquone equivalent to 62.5mg (mg)	125	187.5	250	125	187.5	250	125	187.5	250
Explosol(mg)	30	30	30	-	-	-	-	-	-
Primellose(mg)	-	-	-	30	30	30	-	-	-
Crospopharm(mg)	-	-	-	-	-	-	30	30	30
Magnesium Stearate(mg)	4	4	4	4	4	4	4	4	4
Talc(mg)	4	4	4	4	4	4	4	4	4
MCC(mg)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Mannitol	100	100	100	100	100	100	100	100	100
Total wt(mg)	500	500	500	500	500	500	500	500	500

Table 2: Concentration and absorbance obtained for calibration curve of Atovaquone In pH 6.8 Phosphate buffer

S. No.	Concentration (µg/ml)	Absorbance* (at 276 nm)
1	0	0
2	2	0.148
3	4	0.267
4	6	0.392
5	8	0.523
6	10	0.675

Table 3: Pre-compression parameters

Formulations	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner ratio	Angle Of Repose(Θ)
F_1	0.41	0.51	17.09	1.09	25.54
F_2	0.46	0.52	16.31	1.11	26.08
F_3	0.43	0.54	15.06	1.14	27.51
F_4	0.42	0.52	14.56	1.13	26.32
F_5	0.44	0.55	17	1.22	27.93
F_6	0.52	0.52	18.01	1.14	28.05
F_7	0.43	0.50	15.94	1.20	26.43
F_8	0.41	0.54	16	1.15	25.67
F_9	0.49	0.56	16	1.16	26.54

Table4: Post-Compression parameters

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Disintegration Time (sec)	Friability (%)	Assay (%)
F1	503	2.6	3.58	48	0.46	98.65
F2	501	2.7	3.61	56	0.47	99.21

F3	502	2.8	3.51	49	0.42	97.42
F4	500	2.5	3.29	52	0.45	97.34
F5	498	2.3	3.60	58	0.42	98.09
F6	501	2.1	3.71	60	0.41	97.21
F7	499	2.6	3.45	72	0.48	98.26
F8	509	2.7	3.42	69	0.49	99.54
F9	500	2.8	3.50	58	0.51	98.32

Table 5: In-vitro dissolution studies of all formulations

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	11.43	23.54	21.09	23.54	22.28	21.09	20.13	18.54	17.45
10	35.24	36.98	31.67	36.92	34.21	36.45	32.67	32.12	38.91
20	44.09	45.67	48.52	45.35	43.24	54.72	42.56	45.72	47.31
30	52.81	56.08	59.78	57.32	56.41	63.72	56.08	57.46	56.38
40	63.94	75.32	72.45	66.23	66.29	77.56	63.11	65.32	67.29
50	77.54	83.97	87.62	75.32	74.23	87.09	79.25	75.21	75.65
60	83.21	89.45	97.21	82.45	82.46	93.04	84.91	80.34	81.54

From the tabular column 4.5 it was evident that the formulations prepared with super disintegrate Explosol showed maximum % drug release in 60 min i.e 97.21% (F3 formulations and the concentration of super disintegrate was 30 mg). So the principle of super disintegrates was found to be useful to produce Oral dispersible tablets. F3 formulation was considered as optimized formulation.

4. Conclusion

The main objective of the present work was to improve the solubility and dissolution rate of poorly water soluble anti-hypertensive drug Atovaquone by Solid dispersion technology using hydrophilic polymer poloxamer 407 as carrier. Nine formulations were prepared by employing primellose ,explosol and crospopharm as super disintegrants. The prepared formulations were evaluated and characterized. All the results of pre-compression parameters were found to be satisfactory and post-compression parameters showed good mechanical strength and good uniformity in all formulations. Based on the in-vitro dissolution studies F3 formulation was considered as the optimized formulation since it has shown the maximum drug release of 97.21% in 60mins compared to all other formulations.

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