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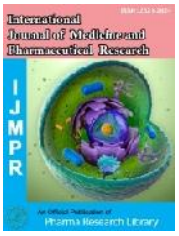

Research Article **Open Access**

Formulation and *In-vitro* Evaluation of Atovaquone Solid Dispersions

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A B S T R A C T

In the current study improvement of dissolution rate, solubility and bioavailability of insoluble drug Atovaquone was done by solid dispersions prepared by using hydrophilic and lipophilic carriers. PVP, PEG 5000, Poloxamer 188 were selected as hydrophilic carriers and Gelucire 44/14 and Gelucire 50/13 were selected as lipophilic carriers to enhance the dissolution rate, solubility and hence bioavailability. Aerosil 380 was selected as inert carrier in case of solid dispersions prepared with lipophilic carriers. Ratio of drug to polymer was varied from 1:1 to 1:5. Melting and Solvent evaporation method was followed. From the results of comparative dissolution studies conducted between optimized formulations, pure drug and marketed formulations, it was concluded that formulations prepared with gelucire 44/14 (ASD 24) have shown greater drug release than remaining formulations.

Keywords: Atovaquone, Solvent evaporation method, solid dispersions.

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1. Introduction

Solid dispersions were first demonstrated in 1961 by Sekiguchi K and Obi N. The term solid dispersion is used to describe the mixture of a poorly soluble drug in an inert, water soluble carrier, usually prepared via the melt or solvent methods. Solid dispersions are able to enhance the dissolution behaviour of poorly water soluble drugs and also therefore improve their *in vivo* bioavailability. Atovaquone is a unique naphthoquinone with broad-spectrum antiprotozoal activity. It is effective for the treatment and prevention of Pneumocystis carinii

pneumonia (PCP), Malaria and Babesiosis .In spite of this wide spectrum of pharmacological activity, its use in pharmaceutical field is limited because it suffers from low aqueous solubility (less than 0.0002mg/ml at 25˚C) and belongs to class II of the biopharmaceutical classification system (BCS). As a result it exhibits poor dissolution and insufficient oral bioavailability.

2. Materials and Methods

Atovaquone, PVP, PEG, Poloxamer, Gelucire, Aerosil 380, chemicals were Laboratory grade made of SD Fine chemicals Pvt Ltd

Formulation Development of Solid Dispersions of Atovaquone: Solid dispersions of Atovaquone were prepared by using different hydrophilic/lipid based carriers such as PVP, PEG, Poloxamer 188, gelucire 44/14 and gelucire 50/13 in different ratios such as 1:1,1:2 &1:3. These ratios were decided based on the results obtained in phase solubility studies. Composition of prepared solid dispersions are given in tables1-5.

UV Visible Spectroscopic method to estimate Atovaquone from *in vitro* samples

Calibration curve of Atovaquone was plotted by using UV visible spectroscopic method at 234 nm. Linearity was observed between 2-16 µg/mL. Absorbance values obtained are given in table 6 and calibration curve plotted is shown in figure 1. Regression equation obtained was used to estimate the Atovaquone from in vitro samples

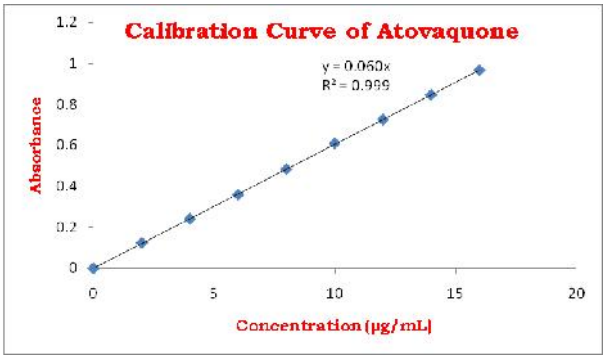

Figure 1: Calibration Curve of Atovaquone

3. Results and Discussion

Characterization of Atovaquone Solid Dispersions

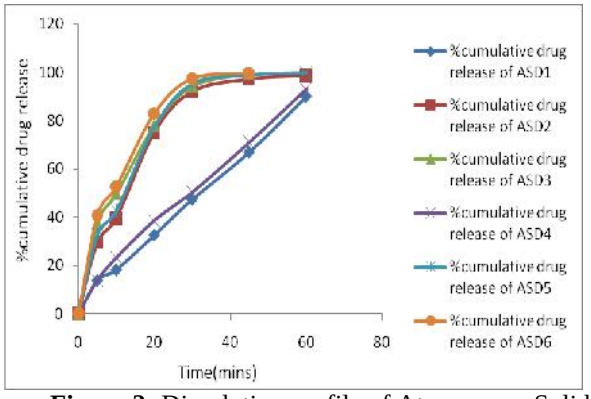

Figure 2: Dissolution profile of Atovaquone Solid Dispersions with PVP

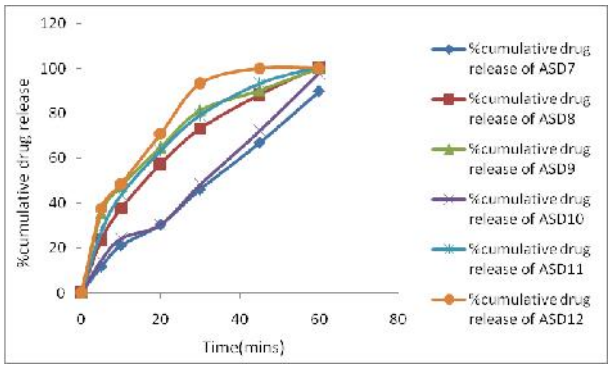

Figure 3: Dissolution profile of Atovaquone Solid Dispersions with PEG

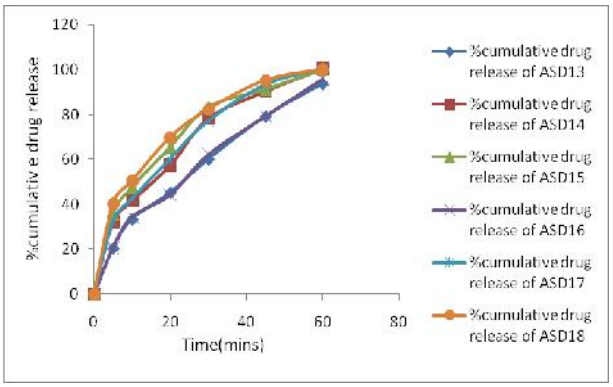

Figure 4: Dissolution profile of Atovaquone Solid Dispersions with Poloxamer

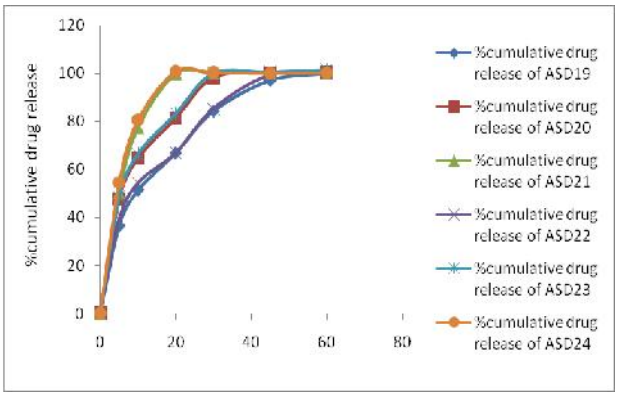

Figure 5: Dissolution profile of Atovaquone Solid Dispersions with Gelucire 44/14

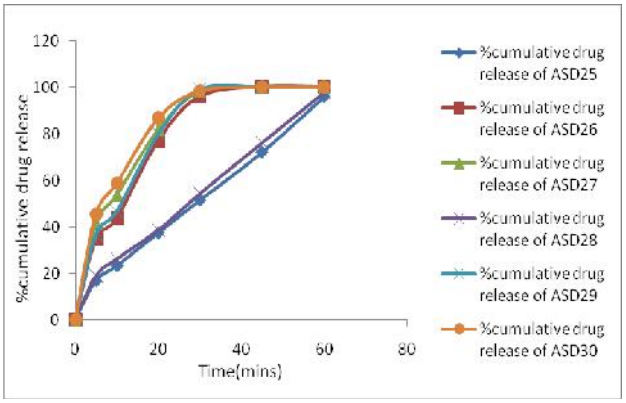

Figure 6: Dissolution profile of Atovaquone Solid Dispersions with Gelucire 50/13

Micromeritic evaluation:

The prepared solid dispersions were characterized for their micromeritic properties. Results are tabulated in table no 7. It was observed that flow property was improved with all the formulations compared to pure drug.

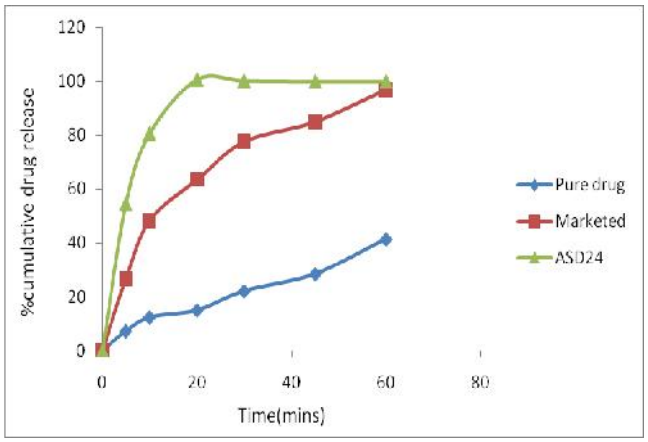

Figure 7: Comparative dissolution profile of Atovaquone

Ex vivo permeation studies

Ex vivo permeation studies were conducted for 3 hrs by using goat intestinal membrane for the best formulation, pure drug and marketed formulations. Amount of drug diffused at various time intervals was calculated and the results obtained were given in the Table11. Graph was plotted by taking amount of % drug permeated on Y-Axis and time on X-axis and shown in Figure8. From the results it was noticed that best formulation have shown greater amount of drug permeation through membrane than the marketed and pure drug at each time interval.

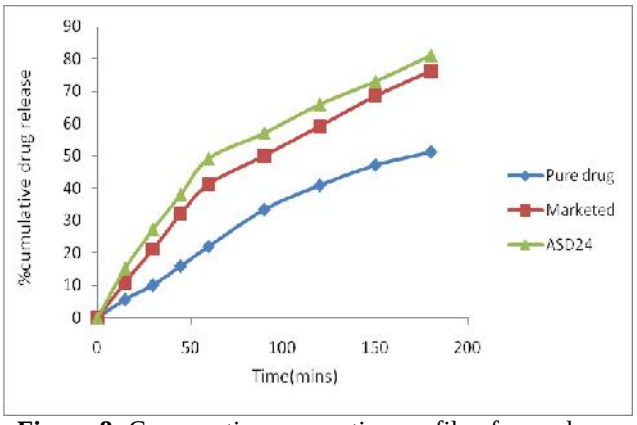

Figure 8: Comparative permeation profile of pure drug, marketed and best formulation (ASD24)

4. Conclusion

In the current study improvement of dissolution rate, solubility and bioavailability of insoluble drug Atovaquone was done by solid dispersions prepared by using hydrophilic and lipophilic carriers. PVP, PEG 5000, Poloxamer 188 were selected as hydrophilic carriers and Gelucire 44/14 and Gelucire 50/13 were selected as lipophilic carriers to enhance the dissolution rate, solubility and hence bioavailability. Aerosil 380 was selected as inert carrier in case of solid dispersions prepared with lipophilic carriers. Ratio of drug to polymer was varied from 1:1 to 1:5. Melting and Solvent evaporation method was followed. From the results of comparative dissolution studies conducted between optimized formulations, pure drug and marketed formulations, it was concluded that formulations prepared with gelucire 44/14 (ASD 24) have shown greater drug release than remaining formulations.

Table 1: Solid dispersions of Atovaquone prepared with PVP

Frmulation Code	Drug (mg)	Carrier (PVP) (mg)	Ratio	Method
ASD1	250	125	1:1	Melting
ASD2	250	250	1:2	Melting
ASD 3	250	370	1:3	Melting
ASD 4	250	125	1:1	Solvent Evaporation
ASD 5	250	250	1:2	Solvent Evaporation
ASD 6	250	370	1:3	Solvent Evaporation

Table 2: Solid dispersions of Atovaquone prepared with PEG 5000

Frmulation Code	Drug (mg)	Carrier (PEG) (mg)	Ratio	Method
ASD 7	250	125	1:1	Melting
ASD 8	250	250	1:2	Melting
ASD 9	250	370	1:3	Melting
ASD 10	250	125	1:1	Solvent Evaporation
ASD 11	250	250	1:2	Solvent Evaporation
ASD 12	250	370	1:3	Solvent Evaporation

Table 3: Solid dispersions of Atovaquone prepared with Poloxamer 188

Frmulation Code	Drug (mg)	Carrier (Poloxamer) (mg)	Ratio	Method
ASD 13	250	125	1:1	Melting

ASD 14	250	250	1:2	Melting
ASD 15	250	370	1:3	Melting
ASD 16	250	125	1:1	Solvent Evaporation
ASD 17	250	250	1:2	Solvent Evaporation
ASD 18	250	370	1:3	Solvent Evaporation

Table 4: Solid dispersions of Atovaquone prepared with Gelucire 44/14

Frmulation Code	Drug (mg)	Carrier (Gelucire) (mg)	Inert Carrier (Aerosil 380) (mg)	Ratio	Method
ASD 19	250	125	125	1:1	Melting
ASD 20	250	250	250	1:2	Melting
ASD 21	250	370	370	1:3	Melting
ASD 22	250	125	125	1:1	Solvent Evaporation
ASD 23	250	250	250	1:2	Solvent Evaporation
ASD 24	250	370	370	1:3	Solvent Evaporation

Table 5: Solid dispersions of Atovaquone prepared with Gelucire 50/13

Frmulation Code	Drug (mg)	Carrier (Gelucire) (mg)	Inert Carrier (Aerosil 380) (mg)	Ratio	Method
ASD 25	250	125	125	1:1	Melting
ASD 26	250	250	250	1:2	Melting
ASD 27	250	370	370	1:3	Melting
ASD 28	250	125	125	1:1	Solvent Evaporation
ASD 29	250	250	250	1:2	Solvent Evaporation
ASD 30	250	370	370	1:3	Solvent Evaporation

Table 6: Calibration curve of Atovaquone

Concentration (µg/mL)	Absorbance (at 234 nm)
0	0.000
2	0.124
4	0.241
6	0.358
8	0.482
10	0.608
12	0.724
14	0.845
16	0.964

Table 7: Micromeritic properties of Atovaquone Solid Dispersions

S.NO.	Angle of Repose (^{0})	Tapped Density (g/cc)	Bulk Density (g/cc)	Consolidation Index (%)	Hausner's Ratio
ASD1	$27^0 12'' \pm 12''$	0.89±0.01	0.74 ± 0.03	14.5± 0.11	1.16± 0.01
ASD2	$28^0 45'' \pm 18''$	0.84±0.03	0.72± 0.03	14.2± 0.34	1.18 ± 0.02
ASD3	$29^0 12'' \pm 32''$	0.82± 0.04	0.72± 0.05	12.5± 0.84	1.16± 0.03
ASD4	$29^0 54'' \pm 45''$	0.83±0.04	0.71± 0.06	12.1± 0.35	1.14 ± 0.04
ASD5	$30^0 12'' \pm 44''$	0.81±0.03	0.74± 0.01	12.3± 0.31	1.12 ± 0.03
ASD6	$27^0 19'' \pm 23''$	0.77±0.06	0.68± 0.03	12.7± 0.36	1.15 ± 0.09
ASD7	$26^0 12'' \pm 17''$	0.74±0.03	0.67± 0.09	13.2± 0.25	1.13 ± 0.05
ASD8	$29^0 52'' \pm 32''$	0.74±0.04	0.66 ± 0.09	13.3± 0.65	1.18± 0.07
ASD9	$26^0 18' \pm 15''$	0.77±0.06	0.68 ± 0.02	12.6± 0.76	1.15± 0.08
ASD10	$26^0 52'' \pm 14''$	0.72±0.05	0.62 ± 0.03	14.3± 0.77	1.14± 0.03
ASD11	$26^0 81'' \pm 12''$	0.71±0.07	0.58 ± 0.02	14.3± 0.57	1.18± 0.02

ASD12	$29^0 52'' \pm 52''$	0.68±0.03	0.57 ± 0.02	14.6± 0.98	1.17± 0.03
ASD13	$28^0 42'' \pm 61''$	0.66±0.04	0.54± 0.02	15.4± 0.87	1.18± 0.02
ASD14	$28^0 53'' \pm 60''$	0.63±0.05	0.53± 0.03	15.7± 0.75	1.19± 0.02
ASD15	$26^0 32'' \pm 32''$	0.62±0.03	0.52± 0.05	16.2± 0.65	1.19± 0.04
ASD16	$32^0 31'' \pm 53''$	0.69±0.03	0.57± 0.06	14.7± 0.64	1.19± 0.04
ASD17	$26^0 22'' \pm 34''$	0.68±0.03	0.58± 0.06	15.3± 0.98	1.16± 0.05
ASD18	$28^0 21'' \pm 15''$	0.66±0.05	0.56± 0.06	15.2± 0.85	1.16± 0.04
ASD19	$32^0 32'' \pm 11''$	0.85± 0.02	0.75± 0.02	14.6± 0.85	1.13± 0.06
ASD20	$2611'' \pm 19''$	0.62± 0.03	0.53± 0.03	14.9± 0.76	1.18± 0.05
ASD21	$27^0 11'' \pm 12''$	0.85±0.01	0.75 ± 0.02	14.7± 0.14	1.16± 0.01
ASD22	$29^0 52'' \pm 19''$	0.86±0.04	0.76± 0.04	14.1± 0.32	1.17 ± 0.02
ASD23	$26^0 21'' \pm 81''$	0.67± 0.03	0.56± 0.05	12.6± 0.76	1.13± 0.02
ASD24	$26^0 31'' \pm 17''$	0.63± 0.06	0.53± 0.08	12.3± 0.84	1.12± 0.06
ASD25	$26^0 52'' \pm 72''$	0.66± 0.04	0.58± 0.08	12.2± 0.85	1.16± 0.05
ASD26	$25^0 11'' \pm 11''$	0.76± 0.03	0.68± 0.02	12.9± 0.61	1.13± 0.04
ASD27	$29^0 31'' \pm 12''$	0.75± 0.06	0.69± 0.07	13.1± 0.75	1.15± 0.06
ASD28	$30^0 0'' \pm 81''$	0.72± 0.08	0.63± 0.09	13.1± 0.75	1.16± 0.08
ASD29	$28^0 3'' \pm 32''$	0.71± 0.08	0.66± 0.03	12.9± 0.96	1.16± 0.04
ASD30	$27^0 21'' \pm 53''$	0.67± 0.07	0.59± 0.04	14.3± 0.92	1.16± 0.05

Table 8: *In Vitro* Drug Release Data of Atovaquone Solid Dispersion Formulations (n=3)

Formulations	**% Drug Released within (MEAN ± SD)**					
	5 min	**10 min**	**20 min**	**30 min**	**45 min**	**60 min**
ASD1	13.72± 1.56	18.12± 1.14	32.44± 2.47	47.33± 1.71	67.03 ± 1.01	**90.03 ± 1.01**
ASD2	29.62 ± 1.45	39.52 ± 1.85	75.19± 2.26	92.16± 2.22	97.27± 1.44	**98.81± 1.42**
ASD3	37.53± 1.37	49.67± 1.18	77.92± 1.81	94.30± 2.02	99.55± 1.64	**--**
ASD4	13.71± 1.74	23.11± 1.15	38.47± 2.47	50.34± 1.76	71.01 ± 1.01	**93.08 ± 1.02**
ASD5	32.53 ± 1.47	42.52 ± 1.88	77.28± 2.27	95.17± 2.25	98.79± 1.36	**99.73± 1.55**
ASD6	40.56± 1.38	52.69± 1.19	82.92± 1.86	97.30± 2.04	99.45± 1.69	**--**
ASD7	11.70± 1.37	21.12± 1.18	30.44± 2.47	46.25± 1.76	67.04 ± 1.01	**90.04 ± 1.00**
ASD8	23.61 ± 1.45	37.54 ± 1.88	57.39± 2.28	73.16± 2.25	88.27± 1.45	**100.72± 1.44**
ASD9	35.54± 1.48	47.57± 1.24	64.92± 1.83	81.30± 2.03	90.26± 1.74	**100.12± 2.45**
ASD10	14.45± 1.56	24.12± 1.16	30.44± 2.47	48.25± 1.75	72.25 + 3.24	**98.04 ± 3.64**
ASD11	27.24 ± 1.54	43.64 ± 2.12	63.32± 2.55	79.16± 2.32	93.27± 3.78	**100.82± 2.64**
ASD12	37.54± 2.35	48.57± 1.27	70.90± 1.96	93.34± 2.06	100.06± 2.55	**100.25± 2.36**
ASD13	20.61 ± 1.46	33.52 ± 1.87	45.27± 2.29	60.18± 2.29	79.27± 1.39	**93.82± 1.46**
ASD14	32.01 ± 2.45	41.54 ± 1.89	57.29± 2.27	78.16± 2.29	90.27± 3.45	**100.24± 1.49**
ASD15	35.54± 1.49	47.57± 1.28	65.50± 1.94	83.30± 2.05	91.17± 1.76	**100.21± 2.44**
ASD16	20.62 ± 1.46	34.55 ± 1.88	44.27± 2.29	62.17± 2.28	79.27± 1.48	**95.85± 1.49**
ASD17	32.52 ± 2.45	42.54 ± 1.97	60.29± 2.47	77.16± 2.36	93.27± 3.46	**100.54± 3.47**
ASD18	40.30± 1.47	50.47± 2.33	69.90± 2.96	82.30± 2.26	95.17± 1.97	**100.11± 2.56**
ASD19	36.42± 1.46	51.34± 2.36	66.90± 2.82	84.30± 2.51	97.17± 2.96	**100.18± 2.59**
ASD20	47.55 ± 2.49	64.53 ± 2.97	81.29± 2.98	98.17± 2.58	100.21± 2.56	**100.54± 3.49**
ASD21	50.34± 1.46	77.47± 2.34	99.90± 1.96	100.30± 2.24	100.14± 2.55	**100.15± 2.53**
ASD22	39.41± 1.56	54.37± 2.34	66.92± 2.86	85.32± 2.55	99.27± 2.75	**100.18± 2.56**
ASD23	48.65 ± 2.51	66.56 ± 2.96	83.29± 2.96	100.11± 2.47	100.36± 2.45	**101.52± 2.47**
ASD24	54.45± 1.27	80.57± 2.39	100.80± 1.94	100.32± 2.44	100.11± 2.55	**100.13± 2.44**
ASD25	16.78± 1.46	23.14± 1.17	37.39± 2.44	51.35± 1.74	72.04 ± 1.00	**96.04 ± 1.01**
ASD26	34.66 ± 1.47	43.57 ± 1.88	77.19± 2.23	96.16± 2.25	100.29± 1.46	**100.23± 1.44**
ASD27	41.54± 1.55	53.67± 1.197	81.80± 1.84	98.30± 2.14	100.24± 1.64	**100.15± 1.35**
ASD28	18.78± 1.36	26.15± 1.17	38.59± 2.49	54.25± 1.75	76.24 ± 1.02	**98.04 ± 1.02**
ASD29	36.66 ± 1.55	46.67 ± 1.79	79.98± 2.23	99.18± 2.27	100.18± 1.48	**100.33± 1.46**
ASD30	**45.45± 1.68**	**58.76± 1.12**	**86.90± 1.88**	**98.50± 2.26**	**100.15± 1.53**	**100.25± 1.52**

Table 9: Comparative dissolution profile of pure drug, marketed and best formulation

Time (min)	% Drug Released		
	Pure drug	Marketed	ASD24
0	0	0	0
5	7.14±0.52	26.54±1.54	54.45± 1.27
10	12.24±1.22	48.24±1.02	80.57± 2.39
20	14.89±1.09	63.43±1.62	100.80± 1.94
30	21.97±0.87	77.54±1.69	100.32± 2.44
45	28.39±0.87	84.96±1.26	100.11± 2.55
60	41.43±0.24	96.89±1.34	100.13± 2.44

Table 10: Dissolution parameters of pure drug, marketed and best formulation (LSD24)

Parameters	Q_{10}[a]	Q_{60}[a]	DE_{10}[b]	DE_{60}[b]	MDT[c]	MDR[c]	IDR[c]	$t_{50\%}$[c] (min)
Pure Drug	12.24	41.43	6.72	16.33	51.16	0.71	1.23	>60
Marketed	47.24	97.89	10	56.67	15.34	2.58	2.96	17.2
Best formulation (LSD24)	80.57	100.13	26.66	80	13.71	3.59	4.44	< 5

Table 11: Comparative permeation study data of pure drug, marketed & best formulation (LSD24)

Time (min)	% Drug Permeated		
	Pure drug	**Marketed**	**ASD24**
0	0	0	0
15	5.714±0.28	11.04±0.35	15.291±1.6
30	10.138±0.56	21.241±1.3	27.333±0.36
45	16.025±1.25	32.041±2.35	38.11±0.9
60	21.986±0.25	41.26±0.65	49.215±1.6
90	33.44±1.38	50.09±0.36	57.08±2.36
120	40.922±2.79	59.216±0.25	65.97±2.65
150	47.13±0.23	68.469±0.29	73.05±0.36
180	51.198±1.9	76.250±0.256	81.09±2.10

5. References

[1] Faizan Sayeed, Aejaz Ahmed and Abdul Sayeed Formulation and In Vitro Evaluation of Solid Dispersion Of Fluconazole IJPSR, 2016; Vol. 7(10): 4170-4179.

[2] Nidhi Saini, Rakesh Kumar, Manju Yadav and Kamal Saroha Formulation, Optimization & Evaluation Of Solid Dispersion Based Gastroretentive Floating Tablets Of Cefpodoxime Proxetil IJPSR, 2016; Vol. 7(4): 1734-1739.

[3] Arno A Enose, Priya Dasan, Hariharan Sivaramakrishanan and Vandita Kakkar Formulation, Characterization and Pharmacokinetic Evaluation of Telmisartan Solid Dispersions J Mol Pharm Org Process Res 2016, 4:1

[4] Anusha Pagadala, Madhuri Asiniparthi and Vaidehi Donti Formulation and Evaluation of Solid Dispersion of Glimepiride in to Sustained Release Glob J Pharmaceu Sci 1(2): GJPPS. MS.ID. 55553 (2016)

[5] Ananda Kumar Chettupalli Formulation And Evaluation Of Allopurinol Solid Dispersions By Solvent Evaporation Technique IJPSR (2017), Volume 8, Issue 10

[6] Ganesh Chaulang, Piyush Patel, Sharwaree Hardikar, Mukul Kelkar, Ashok Bhosale, Sagar Bhise Formulation and Evaluation of Solid Dispersions of Furosemide in Sodium Starch Glycolate Tropical Journal of Pharmaceutical Research, February 2009; 8 (1): 43-51

[7] Armin M, Rahman M, Qamrul A, Habibur R, Raihanul I. Enhancement of solubility and dissolution properties of clonazepam by solid dispersions. Asian Journal of Pharmaceutical Research 2012; 2:57-65.

[8] Babu PS, Chowdary KPR. Enhancement of dissolution rate of celecoxib by solid dispersion in superdisintegrants. Indian Drugs 2008; 45:547-552.

[9] Baku E, John EAC, Kristina TN. Study of equilibrium solubility by saturation shake- flask method using hydrochlorthiazide as model compound. Journal of Pharamceutical and Biomedical Analysis 2008; 46:335-341.