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Der Pharmacia Lettre, 2012, 4 (2):683-694
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ISSN 0975-5071
USA CODEN: DPLEB4

Formulation and evaluation of oral fast disintegrating tablets by using amlodipine besylate solid dispersion by direct compression method

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ABSTRACT

Amlodipine Besylate*is a major calcium channel blocker for the treatment of hypertension. In the present study it reveals that the oral fast disintegrating tablet of* Amlodipine Besylate*using different combination of superdisintegrants like Croscarmellose sodium (Ac-Di-Sol), Sodium Starch Glycolate (Primogel), Cross Povidone (Polyplasdone) and got better bioavailability within a short duration of time with different formulations. Although oral disintegrating tablets are much useful in the cases of geriatric, pediatric and travelling patient because no water required for the administration. For the masking of bitter taste we used aspartame as sweetening agent. In this study instead of drug we prepared drug solid dispersion so that drug's solubility we enhanced. Finally F3 and F9 formulation showing more drug release it was found to be 96.67% and 97.33% respectively within 15 min of time.*

Key words: Amlodipine Besylate, Solid dispersion, Superdisintegrants, Direct compression.
Abbreviations: *FTIR-Fourier transform infrared spectroscopy, USP- United States Pharmacopoeia, SD- Solid dispersion, %CDR- Cumulative percentage drug release.*

INTRODUCTION

There were vast no of drugs available for the treatment of hypertension. As it was a complicated disease to cure, the drugs required to be modified to suitable dosage forms for the effective therapeutic action. Apart from the therapeutic action many of the drugs produces sedation and CNS effects which is a major drawback of several drugs. Among all the drugs Amlodipine Besylate is a major drug which is of a calcium channel blocker belonging to the chemical group Di hydro Pyridine. This relieves from the above mentioned disadvantages.,

Advantages of amlodipine over the other drugs
- No effects on plasma lipid profile, uric acid level and electrolyte balance
- No impairment of renal perfusion
- As it does not effect on foetus the drug can be administered at the time of pregnancy.

As we know that the Fast dissolving tablets have the nature of disintergating in a less time. And generally solid dispersions having more bioavailablity when comparing with normal dosage forms.

Basing on these above two principles we developed fast dissolving tablet by using solid dispersion of Amlodipine Besylate.

MATERIALS AND METHODS

2.1.Materials:
Amlodipine besylate and Croscarmellose Sodium (CCS) was a gift sample from Orchid Pharmaceuticals, Chennai. Sodium Starch Glycolate (SSG) and Crospovidone (CP) were obtained from S-d-fine chem, Mumbai. Microcrystalline cellulose, Aspartame and magnesium stearate were purchased from Lobachemie Mumbai. Isopropyl alcohol was obtained from Nice chemicals, Cochin. All other ingredients used were of analytical grade.

2.2 Method:
2.2.1. Experimental design
A 3^2 full factorial design was applied for tablets preparation in which two factors were studied each at three levels. The two factors were the preparation of solid dispersion and comparative study of superdisintegarnts . Three disintegrants were used, each in its optimum concentration as tested before in preliminary studies, Croscarmellose sodium (Ac-Di-Sol), Sodium Starch Glycolate (Primogel), Cross Povidone (Polyplasdone). The compatibility of the chosen excipients was tested using FTIR in a preliminary study. And the FTIR figures were shown in the below Fig A.1, A.2, A.3 and A.4.

2.2.2. Formulation of Solid dispersion:
Solid dispersion were prepared using solvent evaporation methodand the formula was mentioned in the below Table A.1. Here we used chloroform and di chloromethane as solvents for the preparation. We prepared different combinations of solid dispersions by using different superdisintegrants with the drug. And the combinations were mentioned in the given table. Later for evaporation of these solvents which were used for the preparation. We kept in a hot air oven at 40^0C temperature and then it was stored in a desiccator for further use.For getting uniform size of solid dispersion we passed all the solid dispersion through #60 mesh[1].

2.2.3. Dissolution data for the prepared Solid dispersions:
Dissolution study was performed for all the prepared solid dispersion by sing USP-II paddle apparatus. In this 300 ml of saliva phosphate buffer pH 6.8 was used and maintained temp 37 ± 0.5 ^{0}C with 50 rpm. Then 2ml of sample was withdrawn at every 5 min up to 15 min. and then it was analyzed by using UV-Visible spectrophotometer at 367nm and the values were tabled in below Table A.2.

2.2.4. Drug content:
The content of amlodipine besylate in different solid dispersion was estimated using UV-Visible spectrophotometer. An accurately weighed quantity of solid dispersion (equivalent to 10 mg of Amlodipine besylate) was taken and dissolved in 10ml of methanol. From this solution 1ml of solution was diluted to 10ml and assayed for drug content at 367 nm and the values were tabled below Table A.3.

2.2.5. Preparation of Tablets:
Formulation chart for the prepared solid dispersions along with excipients were mentioned in the Table A.4.
All the materials were passed through #60 sieve prior to mixing. The solid dispersion was properly mixed with Disintegrants, and then with the diluent mannitol. The mixture was mixed with aspartame, menthol,talc and magnesium stearate. The material was then subjected to direct compression in 10 station rotary tablet. Shape: Round, Flat, plain on both sides. Size of punches: 6mm round.

2.2.6.Evaluation of pre compression parameters (Pre formulation studies):
Bulk density:
Bulk densitywas measured by using measuring cylinder. A suitable amount of powder from each formulation, previously flippantly shaken to halt agglomerates formed, was introduced into a 10 ml measuring cylinder. And later the weight and the bulk volume occupied by the test sample was measured and bulk density was determined by using the following formula[2],

Bulk density = {weight of the powder (mg) / bulk volume of the powder (with void spaces)(ml)}.

True density:
he above tested measuring cylinder was tapped about several times and later its true volume was measured and true densitywas measured by using the following formula[2],

True density = {weight of the powder (mg)/ true volume of the powder (without void spaces) (ml)}.

Carr's index (compressibility index):
It was determined by using the above determined bulk density and true densities using the following formula[2],

Carr's index (%) = {(tapped density-bulk density)/tapped density}*100.

Hausner's ratio:
It was also determined by using the above tapped and bulk density values using the following formula[3],

Hausner's ratio ={tapped density / bulk density}.

Angle of repose:
Angle of repose (θ)was determined using funnel method. The blend test sample powder was passed through a funnel that can be elevated perpendicularly until a maximum pinecone height (*h*) was obtained. The radius of the pile (*r*) was measured and angle of repose was calculated[3].

$$(\theta) = \tan^{-1}(h/r).$$

2.2.7. Evaluation of post compression parameters:
Thickness:
It was measured by using Digital Vernier Calipers. Ten tablets from prepared formulation randomly taken and thicknesswas measured[4].

Weight variation:
By following USP monographs it was calculated. In this 20 tablets from the each formulation randomly taken and their total average weight was calculated and then the individual tablet weight was calculated by comparing with the average weight[4].

Hardness:
Hardness was calculated by using Pfizer hardness tester[4].

Friability test:
By following USP monograph this test was calculated. It was measured by using Roche Friabilitor. In this 20 tablets from the each formulation was randomly taken and weighed and then placed all those 20 tablets in the plastic chamber of the Roche Friabilitor and then it was attached to a motor for rotating with a speed of 25 rpm for 4 min and then after 4 min all the 20 tablets weight was determined and friability was calculated[5].

Disintegration time/ Dispersion time:
This was determined by using glass beaker containing 6 ml of saliva buffer pH 6.8. Firstly 6 tablets from the each formulation were randomly taken and dispersion time was calculated[5].
Drug content:
This was testedby taking 10 mg equivalent of Amlodipine besylate was taken from the all formulation and then it was dissolved in 10 ml of methanol. Form that 1 ml was pipetted out and it was make up to 10 ml using methanol and then its absorbance was calculated using UV-Visible Spectrophotometer at 367nm of wavelength[4].

Wetting time:
Wetting timeof the tablets was dignified using a piece of tissue paper (12 cm X 10.75 cm) folded twice, placed in a small Petri dish having diameter of 6.5 cm and containing 6 ml of Saliva buffer (pH 6.8). A tablet was placed on the double folded tissue paper, and the time for the complete wetting was measured[6].

Water absorption ratio:
It was tested by using double folded tissue paper and the petri dish contains 6ml of Saliva buffer pH 6.8. Firstly randomly taken tablets form the all formulations weight was calculated it was denoted as Wb and then the tablets were allowed to place on the tissue paper. After completely wet of the tablet weight was calculated and it was denoted as Wa. And by using the following formula water absorption ratio (R) was measured[6].

$$R = 100 \{ (Wa – Wb) / Wb\}$$

Where,
Wb = Weight of tablet before absorption
Wa = Weight of tablet after absorption.

***In vitro* dissolution test:**
In vitro dissolution studies for all the prepared formulations were carried by randomly picking the tablets from each formulation. This test was carried out using USP type II paddle apparatus at 50rpm using 300ml of Saliva phosphate buffer pH 6.8 as dissolution media, maintained at 37 ± 0.5 ^{0}C. 1ml aliquots were withdrawn at the specified time intervals, filtered through whatmann filter paper and absorbance was calculated using UV-Visible spectrophotometer at 367 nm. An equal volume of fresh medium, which was pre-warmed at 37 ± 0.5 ^{0}C, was replaced into the dissolution media after each sampling to maintain the constant volume thought the test.

Table A.1. Solid dispersions Formulation table

Ingredients	SD1 (mg)	SD2 (mg)	SD3 (mg)
Amlodipine Besylate	10	10	10
Croscarmellose sodium (Ac-Di-Sol)	-	10	10
Sodium Starch Glycolate (Primogel)	10	10	-
Cross Povidone (Polyplasdone)	10	-	10

Table A.2. Dissolution data for the prepared solid dispersions

Time (min)	% CDR from the prepared solid dispersions		
	SD1	SD2	SD3
0	0±0	0±0	0±0
5	71.9±0.9	62.5±0.4359	74.57±0.3512
10	86.5±0.6557	74.57±1.250	90.73±1.250
15	96.47±0.6429	82.07±1.901	98.7±0.3606

Table A.3. Drug content for the prepared Solid dispersions

Character	SD1	SD2	SD3
Drug content	98±0.2	86.02±1.709	97.97±0.4509

Table A.4. Formulations chart

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Drug Solid dispersion	10	10	10	10	10	10	10	10	10
Croscarmellose sodium (Ac-Di-Sol)	4	6	8	-	-	-	-	-	-
Cross Povidone (Polyplasdone)	-	-	-	4	6	8	-	-	-
Sodium Starch Glycolate (Primogel)	-	-	-	-	-	-	4	6	8
Mannitol	102	102	102	102	102	102	102	102	102
Avicel PH 102	30	28	26	30	28	26	30	28	26
Aspartame	1	1	1	1	11	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Menthol	1	1	1	1	1	1	1	1	1
Total weight	150	150	150	150	150	150	150	150	150

RESULTS AND DISCUSSION

All the results for the prepared solid dispersion were mentioned in the below Table A.1, A.2 and A.3. And pre compression parameters for the prepared solid dispersion with their excipients were mentioned in the below table A.5. And post compression parameters were mentioned in the below Table A.6, A.7 and A.8. And the figures for the

prepared solid dispersions were mentioned below Fig. A.5 and A.6. And figures for the prepared tablets post compression parameters were mentioned in the below Fig. A.7, A.8, A.9, A.10 and A.11.

Comparatively F9 formulation showing more bioavailability than others that is it got average % CDR was 97.33% in 15 min.

Table A.5. Pre compression parameters

Formulation code	Bulk density ± S.D*	Tapped density ± S.D*	Carr's index ± S.D*	Hausner's ratio ± S.D*	Angle of repose ± S.D*
F1	0.3793±0.007024	0.4433±0.004163	14.42±2.370	1.169±0.03261	39.82±0.2804
F2	0.3927±0.004041	0.4657±0.004041	15.67±1.380	1.186±0.01957	32±0.09504
F3	0.3680±0.002	0.4130±0.003606	10.89±1.025	1.122±0.01286	32.53±0.1102
F4	0.2667±0.08372	0.4437±0.004041	28.85±0.8675	1.406±0.01712	32.06±0.05132
F5	0.3713±0.003055	0.4427±0.005508	16.1±1.685	1.192±0.02421	32.18±0.02646
F6	0.37030.0±025	0.3947±0.006807	6.146±1.806	1.066±0.02054	32.42±0.03
F7	0.3920±0.003606	0.4427±0.006110	11.44±1.113	1.129±0.0143	32.51±0.03606
F8	0.3680±0.002	0.4313±0.003512	14.68±0.2351	1.172±0.003233	31.88±0.4488
F9	0.3763±0.007638	0.4560±0.006557	17.44±2.827	1.212±0.04165	32.12±0.12

**Each value was an average of three determinations (n=3).*

Table A.6. Evaluation parameters for the prepared Tablets
Tablet characteristics:

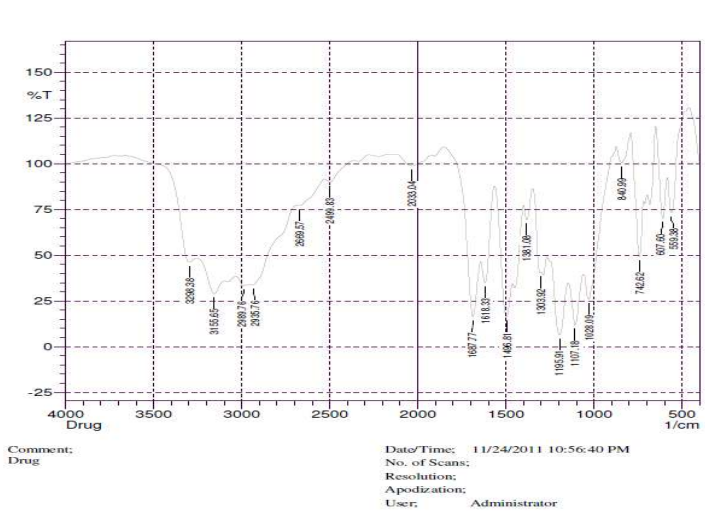
Characteristics	F1	F2	F3	F4	F5	F6	F7	F8	F9
Colour	White	White	White	White	White	White	White	White	White
Odour	Mint	Mint	Mint	Mint	Mint	Mint	Mint	Mint	Mint
Taste	Acrid	Acrid	Acrid	Acrid	Acrid	Acrid	Acrid	Acrid	Acrid
Shape	Flat	Flat	Flat	Flat	Flat	Flat	Flat	Flat	Flat

Table A.7. Evaluation parameters for the prepared Tablets

Formulation code	Thickness ± S.D* (mm) (N=20)	Weight variation ± S.D* (mm) (N=20)	Hardness ± S.D* (Kg/cm^2) (N=10)	Friability ± S.D* (%) (N=20)	Dispersion time ± S.D* (sec) (N=6)	Drug content ± S.D* (N=20)	Wetting time ± S.D* (sec) (N=6)	Water absorption ratio ± S.D*
F1	3.467±0.1155	150.1±0.1155	3.567±0.1155	0.653±0.0305	5.333±0.5774	99.13±0.32	12±2	19.33± 1.528
F2	3.487±0.0230	150±0.01	3.6±0.2	0.653±0.0305	5.333±0.5774	98±1	11±1	15.67±0.5774
F3	3.520±0.02	150.3±0.4359	3.567±0.2082	0.626±0.0305	4.667±0.5774	99.0±0.05	10.6±1.155	14.33±0.5774
F4	3.513±0.0550	151.5±1.286	3.767±0.2517	0.633±0.0230	9.667±2.082	96.9±0.655	20±2	32±2
F5	3.47±0.1473	154.7±2.517	3.633±0.1528	0.65±0.0264	9.333±1.155	95.8±0.763	22±2	35±1
F6	3.47±0.1473	150±0.0152	3.867±0.1155	0.65±0.03	9.333±0.5774	97.5±0.5	22±2	34.33± 0.5774
F7	3.503±0.0568	150.4±0.5532	3.733±0.2082	0.64±0.02	6.667±0.5774	98.2±0.642	13.67±1.52	20.33 0.5774
F8	3.523±0.0251	149±1	3.933±0.1155	0.5867±0.011	5.333±0.5774	98.63±0.55	14±2	15.67±0.5774
F9	3.533±0.1102	150.3±1.528	4±0.2	0.6333±0.023	4.667±0.5774	99.23±0.25	13±1	14±0

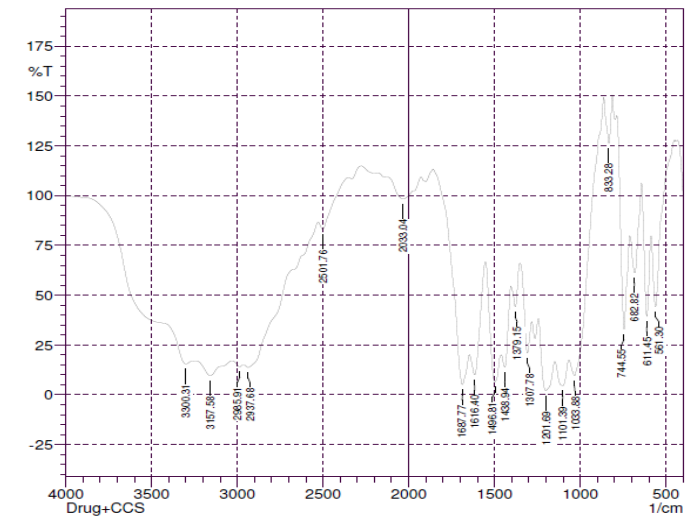
**Each value was an average of three determinations (n=3).*

Fig. A.1 FTIR spectra for the pure Drug (*Amlodipine Besylate*):



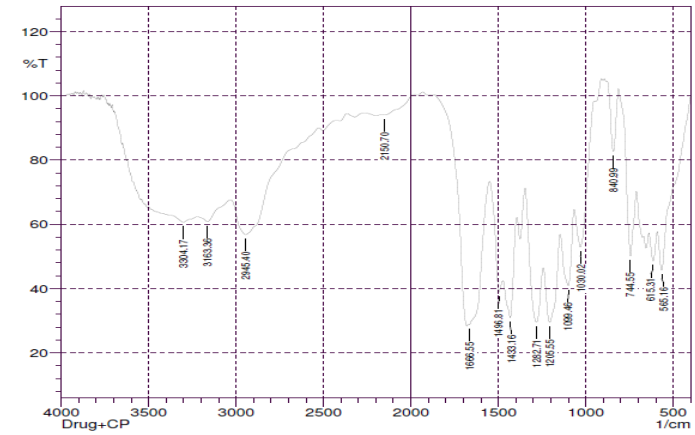
No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	559.38	73.236	27.576	582.52	492.22	0.44	4.225
2	607.6	70.158	32.677	650.03	582.52	3.603	5.175
3	742.62	49.185	42.554	790.84	719.47	9.557	8.457
4	840.99	100.523	11.812	871.85	790.84	-1.977	2.374
5	1028.09	25.896	25.751	1060.88	971.85	43.212	9.81
6	1107.18	11.801	25.253	1147.68	1060.88	54.227	16.885
7	1303.92	6.56	34.146	1265.35	1147.68	78.698	33.486
8	1303.92	40.331	4.1	1346.36	1300.07	11.354	1.131
9	1381.08	69.351	11.114	1398.44	1348.29	5.981	1.64
10	1496.81	16.42	35.712	1562.39	1484.02	44.221	18.375
11	1618.33	35.085	24.544	1643.41	1564.32	22.304	7.381
12	1687.77	16.394	43.147	1847.87	1645.33	43.85	20.709
13	2033.04	98.875	3.68	2119.84	1979.03	-0.576	1.24
14	2499.83	89.887	3.556	2528.76	2362.88	3.193	0.832
15	2669.57	77.116	1.852	2686.93	2530.69	12.816	1.261
16	2935.76	33.731	9.234	2953.12	2688.86	73.777	1.92
17	2989.76	33.341	2.738	3032.2	2955.04	35.304	1.239
18	3155.65	28.959	11.32	3255.95	3101.64	66.864	8.306
19	3298.38	46.086	10.219	3524.06	3257.88	31.729	3.302

Fig. A.2 FTIR spectra of Drug with Croscarmellose sodium (Ac-Di-Sol):



No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	561.3	44.254	44.512	586.38	453.29	8.467	9.519
2	611.45	39.299	51.953	640.39	588.31	11.377	9.321
3	682.82	61.304	28.967	709.83	642.32	7.966	5.636
4	744.55	32.936	73.849	785.05	711.76	13.669	15.225
5	833.28	9.626	23.726	862.21	812.06	-6.794	2.028
6	1033.88	9.626	27.983	1064.74	864.14	69.315	19.46
7	1101.39	4.529	12.533	1147.68	1066.67	86.929	24.62
8	1201.69	2.126	26.408	1244.13	1149.61	105.982	49.09
9	1307.78	20.969	26.652	1350.22	1282.71	29.757	8.887
10	1379.15	44.275	15.514	1402.3	1352.14	14.05	2.993
11	1438.94	13.954	18.384	1458.23	1404.22	33.026	7.565
12	1496.81	6.508	32.07	1552.75	1460.16	67.636	26.88
13	1616.4	10.021	24.966	1645.33	1554.68	55.312	16.453
14	1687.77	5.102	32.955	1857.51	1647.26	79.671	26.729
15	2033.04	98.27	6.919	2125.63	1973.24	-1.45	2.326
16	2501.76	83.145	6.696	2526.83	2351.3	3.143	1.503
17	2937.68	13.684	5.441	2962.76	2528.76	169.119	6.044
18	2985.91	14.053	1.617	3030.27	2964.69	53.504	1.289
19	3157.58	9.643	5.881	3238.59	3093.92	129.373	12.696
20	3300.31	15.44	9.648	3848.12	3240.52	219.597	7.946

Fig. A.3 FTIR spectra of Drug with Cross Povidone (Polyplasdone):



No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	565.16	45.715	17.557	590.24	399.28	29.246	6.457
2	615.31	48.613	8.929	638.46	590.24	13.432	1.86
3	744.55	50.156	30.368	813.99	711.76	14.03	6.69
4	840.99	82.741	20.519	877.64	813.99	2.09	3.014
5	1030.02	52.947	22.596	1066.67	952.87	19.076	8.123
6	1099.46	40.914	20.502	1145.75	1068.6	24.538	7.769
7	1205.55	29.502	20.98	1242.2	1147.68	40.238	12.99
8	1282.71	29.577	26.224	1346.36	1244.13	39.899	15.17
9	1375.29	30.974	21.316	1471.74	1394.58	30.495	8.33
10	1496.81	38.909	12.966	1548.89	1473.66	21.865	2.84
11	1666.55	28.731	0.826	1668.48	1550.82	43.007	4.539
12	2150.7	94.044	0.659	2168.06	1977.1	2.97	0.65
13	2945.4	56.819	14.625	3030.27	2528.76	68.741	14.763
14	3163.36	60.863	3.089	3221.23	3030.27	37.259	1.463
15	3304.17	60.664	1.938	3365.9	3221.23	30.384	0.923

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Drug+CP

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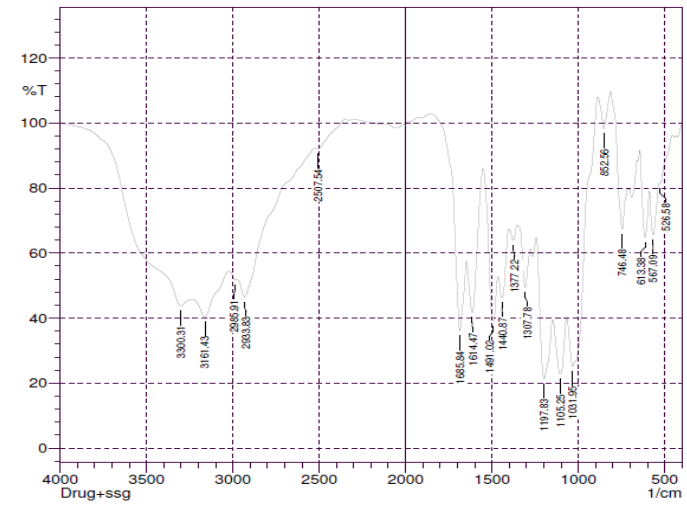
Fig. A.4 FTIR spectra of Drug with Sodium Starch Glycolate (Primogel):



No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	526.58	81.407	0.404	528.51	455.22	3.746	0.059
2	567.09	65.591	14.345	588.31	530.44	8.11	2.59
3	613.38	64.852	19.426	642.32	590.24	7.219	3.412
4	690.54	67.348	22.001	812.06	715.61	7.209	4.333
5	852.56	98.23	10.574	887.28	812.06	-1.248	1.527
6	1031.95	25.057	27.381	1064.74	887.28	51.761	20.226
7	1105.25	22.789	16.891	1147.68	1066.67	42.611	10.085
8	1197.83	21.356	31.313	1242.2	1149.61	45.781	18.173
9	1307.78	49.455	14.876	1352.14	1276.92	17.433	3.288
10	1377.22	63.903	4.17	1402.3	1354.07	8.716	0.66
11	1440.87	46.333	11.799	1462.09	1404.22	15.873	3.093
12	1491.02	39.102	24.19	1548.89	1464.02	22.468	7.708
13	1614.47	41.704	24.946	1645.33	1550.82	22.648	8.317
14	1685.84	36.059	29.949	1853.65	1647.26	26.251	9.078
15	2507.54	92.056	1.129	2524.9	2351.3	2.881	0.338
16	2933.83	46.506	9.001	2974.33	2526.83	67.173	4.512
17	2985.91	51.735	0.655	3022.55	2976.26	12.83	0.113
18	3161.43	40.376	8.39	3232.8	3024.48	69.847	7.094
19	3300.31	43.74	8.366	3742.03	3234.73	110.915	18.738

Comment;
Drug+ssg

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Apodization;
User; Administrator

Fig. A.5 Dissolution data for the prepared solid dispersions

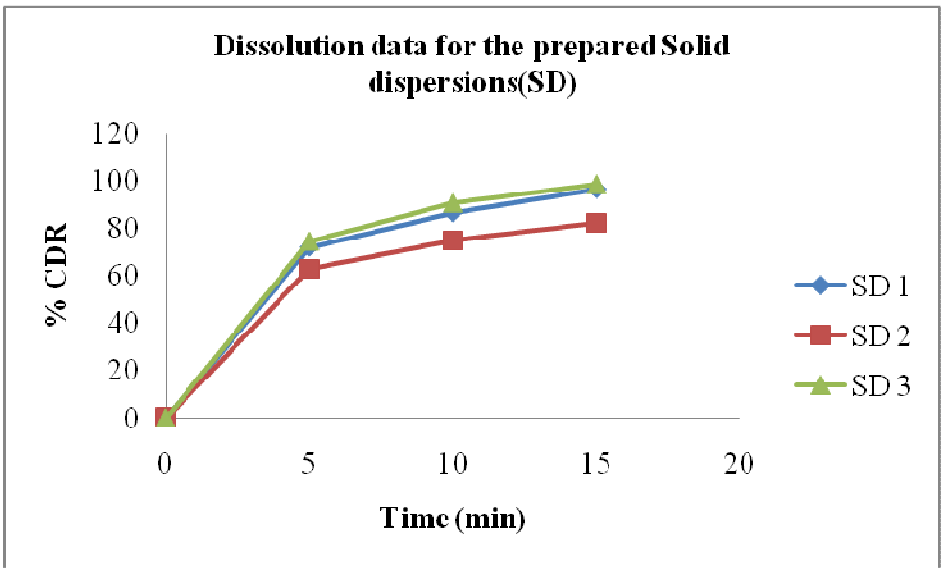

Fig. A.6 Drug content for the prepared solid dispersions

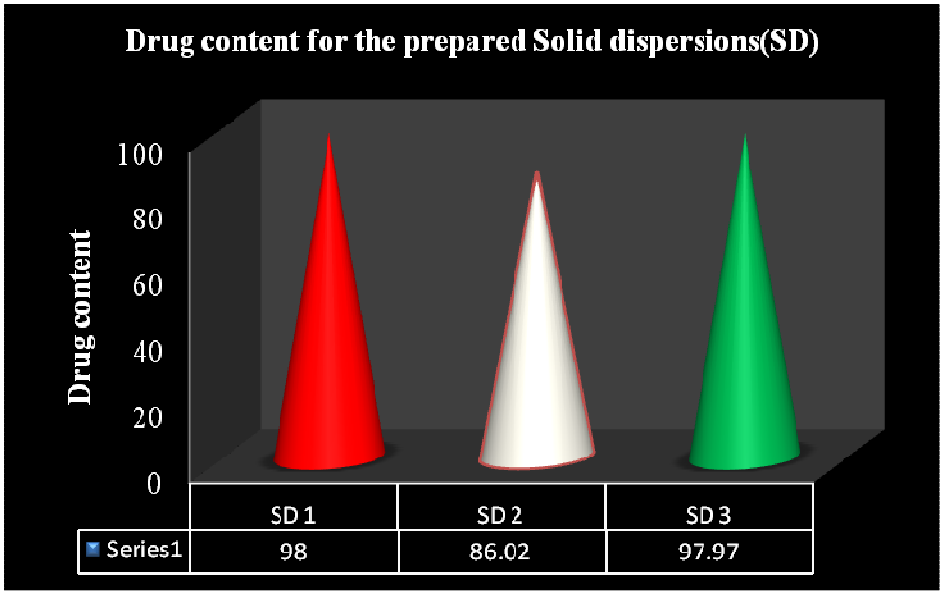

Fig. A.7 Dispersion time for the prepared tablets

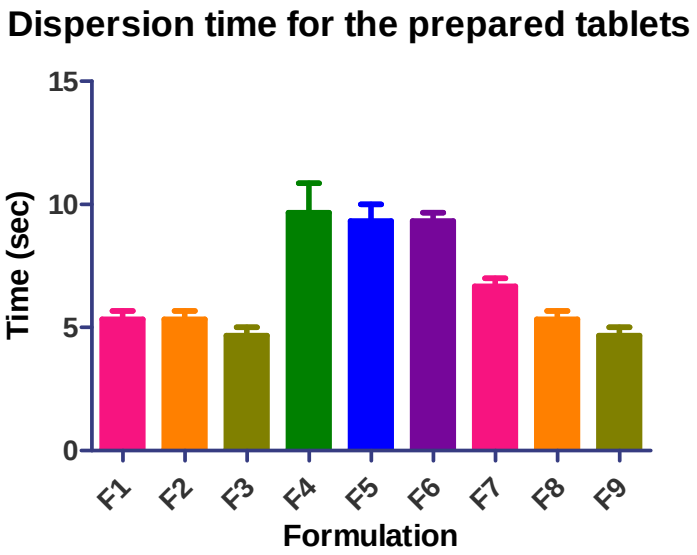

Fig. A.8 Drug content for the prepared tablets

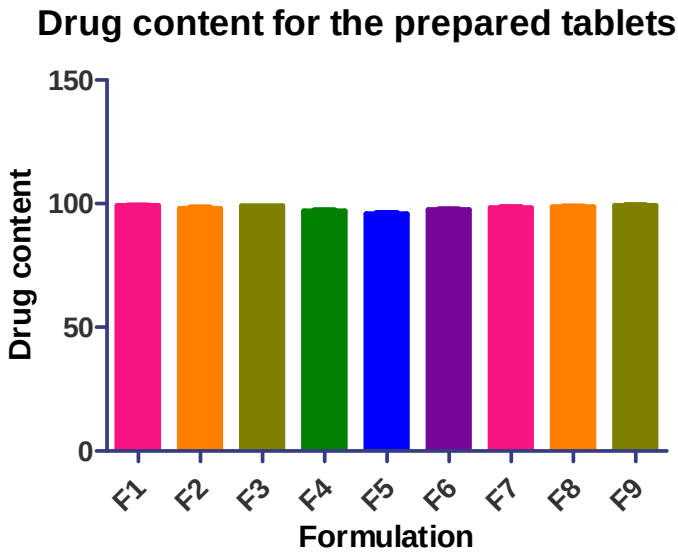

Fig. A.9 Wetting time for the prepared tablets

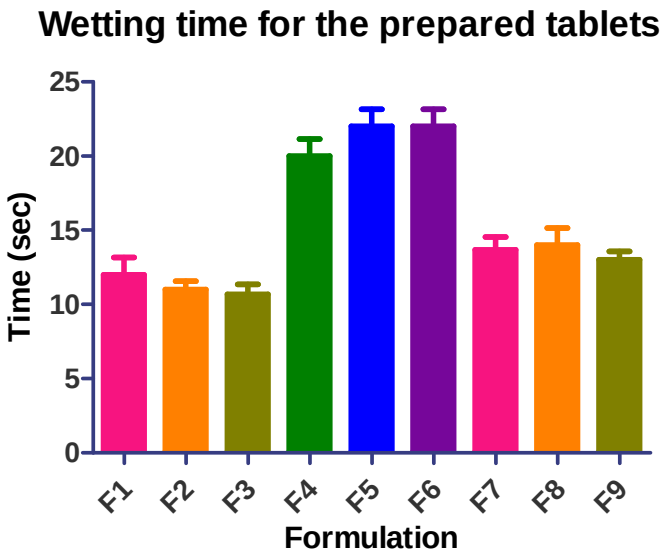

Fig. A.10 Water absorption ratio for the prepared tablets

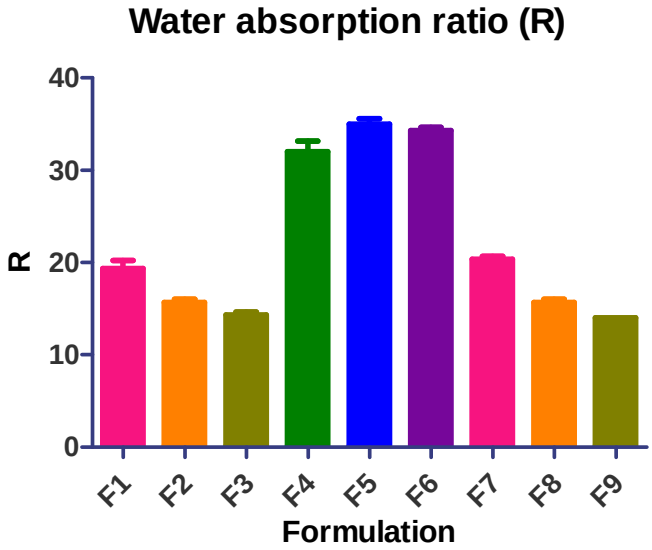

Fig. A.11 Dissolution data for the prepared tablets

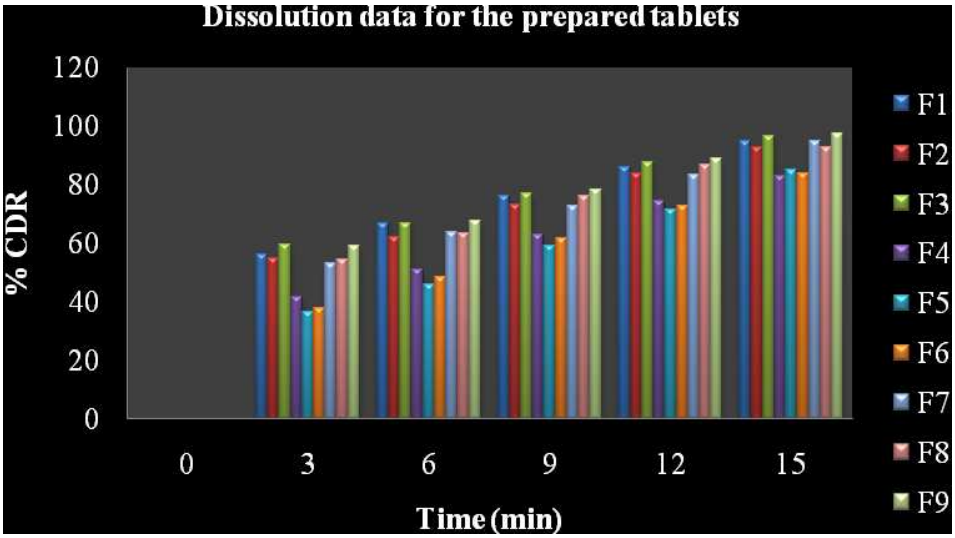

Table A.8.Dissolution data for the prepared Tablets

Time (min)	%CDR± S.D*								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
3	56.33± 0.5774	55± 2	59.67± 1.155	41.67± 1.528	36.67± 1.528	38± 2.646	53± 2	54.33± 1.155	59± 1
6	67± 1	62± 2	67± 2.646	51± 3	46± 3	48.33± 3.512	64± 3.606	63.33± 2.082	67.67± 3.055
9	76.33± 2.309	73.33± 4.163	77± 6.083	63± 3.606	59± 4	61.67± 3.055	73± 1.732	76.33± 3.055	78.33± 3.055
12	86± 3	84± 4.583	87.67± 4.933	74.67± 4.509	71.67± 3.055	73± 6	83.67± 3.215	86.67± 4.933	89± 2.646
15	95± 2.646	93± 3.606	96.67± 3.215	83± 2.646	85± 4.583	84± 4.583	95± 2.646	92.67± 2.517	97.33± 1.528

**Each value was an average of three determinations (n=3).*

CONCLUSION

By this project we are concluding that the mixture of superdisintegrants with the drug in the forms of solid dispersions which are used in the preparation of tablets leads to decrease in the dispersion time and increase in the bioavailability.

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