WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 3, 646-675. Research Article ISSN 2277– 7105

DEVELOPMENT OF AGGLOMERATED CRYSTALS OF OLMESARTAN MEDOXOMIL BY SPHERICAL CRYSTALIZATION TECHNIQUE FOR ENHANCING THE MICROMERITIC AND SOLUBILITY PROPERTY

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Article Received on
22 Dec 2015,

Revised on 13 Jan 2016,
Accepted on 03 Feb 2016

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ABSTRACT

Olmesartan medoxomil practically insoluble in water. The present aim of the work is to increase the solubility by spherical crystallization method and convert into a tablet. N, N dimethyl formamide as a good solvent, bridging solvent chloroform & bad solvent water was selected. Spherical crystals are prepared by using β-cyclodextrin and HP-β-cyclodextrin in various ratios by quasi emulsion solvent diffusion method spherical agglomerates are prepared and converted into orodispersible tablets by direct compression technique. various super disintegrating agents (SSG, Croscarmalose and crospovidone) F18 of 1:3 rations shown high dissolution efficiency of 99%. ANOVA significance value of $P<0.05$ which will indicates the co-processing parameters variability within the specified limits.

KEYWORDS: Olmesartan medoxomil and crospovidone.

INTRODUCTION

The first step in the formulation is often milling or granulation, in order to provide for better properties for the final tabletting or to increase bioavailability. Often very small particles are required in order to increase the dissolution rate, and reach sufficient bioavailability. However, micronisation by milling is extremely inefficient, can cause physical and chemical instability, and produces powders with a wide size distribution and poor flowability. The alternative is to produce quite small crystals directly in the crystallization. In some cases thin

needles are produced having a high surface area to volume ratio, but likewise may be quite difficult to handle. An interesting alternative is to manufacture larger particles in situ by agglomeration of the small crystals during the crystallization. In addition, it has been revealed that agglomerates have properties that make suitable for direct compression tabletting. Crystals could be generated employing any of the available techniques like sublimation, solvent evaporation, vapor diffusion, thermal treatment and crystallization from melt precipitation by change in pH, growth in presence of additives or the grinding.[2] Thus the novel agglomeration technique that transforms crystals themselves directly into a compacted spherical form during crystallization process has been desired.[3] the use of spherical crystallization as a technique appears to be efficient alternative for obtaining suitable particles for direct compression.[4, 5]

This technique of particle design of drugs has emerged as one the areas of active research currently of interest in pharmaceutical manufacturing and recently came into the forefront of interest or gained interest due to the fact that crystal habit can be modified during crystallization process which would result in better micrometric properties like particle size those can enhance the flowability of the powder drug and prepared spherical crystals can be compress directly without performing granulation, drying and so many steps those are require in wet granulation and in dry granulation process of tablet manufacturing.

Spherical crystallization: Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement of flowability and compactability of crystalline drugs.[6]

The various parameters optimized were type, amount and mode of addition of bridging liquid, temperature, and agitation speed to get maximum amount of spherical crystals. These were characterized for micromeritic properties (particle size and shape, flowability), packability (bulk density), wettability (contact angle) and compressibility. It was revealed from the studies that spherical agglomerates exhibited improved solubility, flowability, wettability and compaction behavior.[7, 8]

The present study, an attempt was made to improve physicochemical properties by preparing spherically agglomeration of olmesartan medoxomil in the presence of hydrophilic carrier for the enhancement of overall physicochemical performance. Therefore, in the present study, an

attempt has been made to increase solubility of Olmesartan medoxomil by spherically agglomeration technique.

EXPERIMENTAL WORK

Phase solubility studies of olmesartan medoxomil

Phase solubility studies were performed according to method reported by Higuchi and Connors.[9] Excess (usually more than1mg/mL concentration) of drug was added to each 25mL of different pH Buffer solutions (pH 1.2 to 7.4), distilled water alone and combination with 0.5%, 1%, 2% SLS taken in stopperred conical flasks and mixture were shaken for 24hrs in rotary flask shaker. After shaking to achieve equilibrium, 2ml aliquots were withdrawn at 1hr intervals and filtered through Whatman filter paper. The filtrate was diluted if necessary and analyzed by UV- spectrophotometer at 258 nm. Shaking was continued until three consecutive readings were same.

Phase Solubility Studies of Olmesartan Medoxomil (Pure Drug)

Table No:-1

Solvent	Amount soluble (Olmesartan medoxomil) in mg/ml
0.1N HCl (1.2 pH)	0.108
pH 2.0	0.040
pH 3.0	0.059
pH 4.5	0.061
pH 6.8	0.121
pH 7.4	0.079
Distilled Water	0.0038
Distilled Water + 0.5% SLS	0.078
Distilled Water + 1% SLS	0.081
Distilled Water + 2% SLS	0.085

Preparation of Olmesartan medoxomil Spherical agglomerates: All spherical agglomerates were prepared by the quasi emulsion solvent diffusion method.[10] Olmesartan medoxomil (1g) was dissolved in good solvent N,N-dimethylformamide (25.0 mL). The bridging liquid chloroform (12.5 mL) was added to it. The resulting solution was then poured drop wise in to the poor solvent distilled water (62.5mL) containing Poloxomer F68/ (Gelucire-44/14)/ PVP K-90/ PVA (0.1 g). The mixture was stirred continuously for a period of 20 minutes using a controlled speed mechanical stirrer (Remi motors, India) at 1000 rpm. As the good solvent diffused into the poor solvent, droplets gradually solidified. Finally the co precipitated agglomerates were filtered through Whatman filter paper (No.1) and dried in

desicator at room temperature. The amount of surfactant/polymer added was altered to get desired agglomerates.

Table No:-2

Formulation Number	Olmesartan medoxomil (mg)	β-cyclodextrin (mg) (mg)	HP β-cyclodextrin (mg)	PVP K-90 (mg)	PVA (mg)	N,N-dimethyl Formamide (ml)	Water (ml)	Chloroform (ml)
F1	1000	500	--	--	--	25	62.5	12.5
F2	1000	750	--	--	--	25	62.5	12.5
F3	1000	1000	--	--	--	25	62.5	12.5
F4	1000	--	500	--	--	25	62.5	12.5
F5	1000	--	750	--	--	25	62.5	12.5
F6	1000	--	1000	--	--	25	62.5	12.5
F7	1000	--	--	500	--	25	62.5	12.5
F8	1000	--	--	750	--	25	62.5	12.5
F9	1000	--	--	1000	--	25	62.5	12.5
F10	1000	--	--	--	500	25	62.5	12.5
F11	1000	--	--	--	750	25	62.5	12.5
F12	1000	--	--	--	1000	25	62.5	12.5

Evaluation of spherical agglomerates

a) Particle size determination

Particle size determination was carried out using optical microscopy with a calibrated eye piece micrometer and stage micrometer by taking a small quantity of formulation on slide[84]. About 100 spherical agglomerates size was measured individually, average was taken and their size range and mean diameter frequency was calculated. Average Particle size is calculated by the following formula, Average Particle size= £nd/ n.

b) Solubility studies

The solubility of spherical agglomerates in water was determined by taking excess quantity of spherical agglomerates and adding to screw- capped 50 ml glass vials filled with water. The vials were shaken for two hours on mechanical shaker. The solution was filtered through Whatmann filter paper No.1 and the drug concentration was determined spectrophotometrically at 258 nm.[11]

Solubility studies of Olmesartan medoxomil spherical agglomerates prepared by agglomeration technique

Table No:-3

Formulation	Particle size(µm)	Solubility (mg/ml)
Pure drug	223	0.0038
FI	215	0.0645
F2	247	0.0762
F3	267	0.0889
F4	276	0.0565
F5	293	0.0652
F6	312	0.0773
F7	324	0.0453
F8	347	0.0548
F9	384	0.0667
F10	356	0.0342
F11	374	0.0435
F12	394	0.0554

c) Drug Content Estimation

The percentage drug content in spherical agglomerates was estimated by dissolving 50 mg of spherical agglomerates in methanol, mixed thoroughly by shaking and the volume was made up to the mark with in 6.8 pH phosphate buffer. The solution was filtered and the filtrate was diluted suitably with 6.8 pH phosphate buffer and absorbance was measured at 258 nm using UV/Visible spectrophotometer.[12]

Drug content of Olmesartan medoxomil spherical agglomerates prepared by agglomeration technique

Table No:-4

Formulation	% of Drug content
FI	98.18
F2	97.63
F3	97.23
F4	98.44
F5	97.14
F6	96.27
F7	95.12
F8	93.71
F9	92.19
F10	95.25
F11	94.37
F12	92.16

d) Dissolution studies of agglomerates

In-vitro dissolution studies of pure drug and spherical agglomerates were carried out for 60 minutes using USP Dissolution test apparatus type II (Lab India DISSO 2000, eight stages) at 50 rpm.Spherical agglomerates equivalent to 20 mg of pure drug (Olmesartan medoxomil) used for dissolution study at 37±0.5^0 C in 900ml of 6.8 pH phosphate buffer as dissolution medium. Aliquot equal to 5 ml was withdrawn at regular time intervals (10, 20, 30, 40, 50, 60 min), an equal volume of fresh dissolution medium was replaced to maintain the sink condition and aliquots were measured at 258 nm UV/Visible spectrophotometer. DE_{30}%, T_{50}, T_{90} and k^{-1} values were calculated from dissolution data.[13]

In-vitro dissolution data of Olmesartan medoxomil spherical agglomerates prepared with B-cyclodextrin in different ratios

Table No:-5

S.No.	Sampling time (min)	Cumulative % of drug dissolved ($\overline{X}$ ± S.D.)			
		Pure Drug	F 1	F 2	F3
1	0	0.	0	0	0
2	10	2.69	29.40	34.11	37.25
3	20	4.80	36.37	40.58	44.41
4	30	6.93	51.75	56.34	60.04
5	40	9.76	69.84	74.45	78.06
6	50	11.55	80.01	84.98	88.38
7	60	13.09	87.59	91.56	94.26

Dissolution profiles of Olmesartan medoxomil pure drug and spherical agglomerates prepared with β-cyclodextrin different ratio

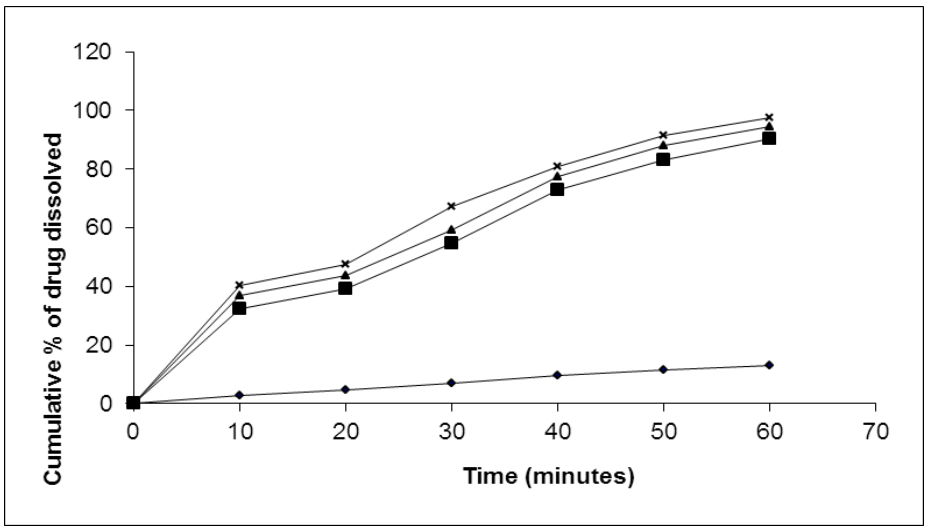

Figure No:-1

(-♦-) Olmesartan medoxomil pure drug

(-■-) Spherical agglomerates prepared with Olmesartan medoxomil and B-cyclodextrin in 1: 0.5 ratio

(-▲-)Spherical agglomerates prepared with Olmesartan medoxomil and B-cyclodextrin in 1: 0.75 ratio

(-×-) Spherical agglomerates prepared with Olmesartan medoxomil and B-cyclodextrin in 1: 1 ratio

First order plots of Olmesartan medoxomil pure drug and spherical agglomerates prepared with B-cyclodextrin in different ratios

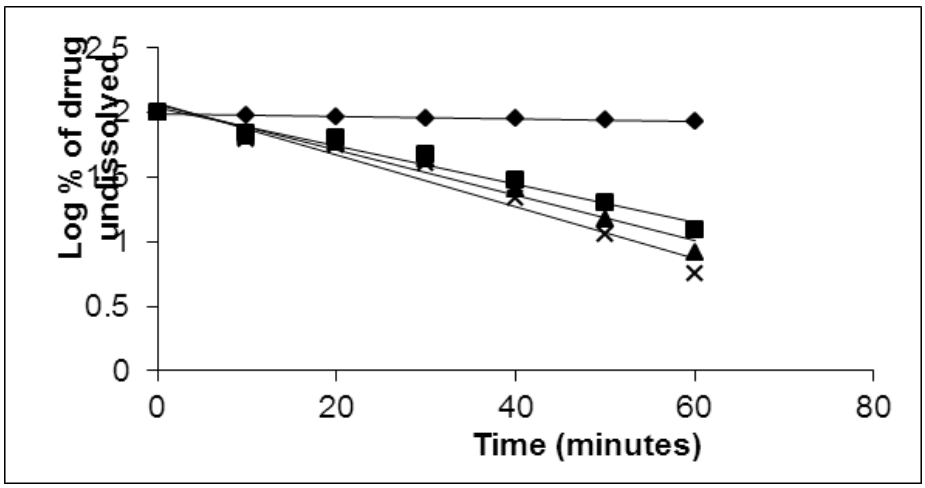

Figure No:-2

(-♦-) Olmesartan medoxomil pure drug

(-■-) Spherical agglomerates prepared with Olmesartan medoxomil and B-cyclodextrin in 1: 0.5 ratio

(-▲-)Spherical agglomerates prepared with Olmesartan medoxomil and B-cyclodextrin in 1: 0.75 ratio

(-×-) Spherical agglomerates prepared with Olmesartan medoxomil and B-cyclodextrin in 1: 1 ratio

***In-vitro* dissolution kinetics of Olmesartan medoxomil spherical agglomerates prepared with β-cyclodextrin 8 in different ratios**

Table No:-6

S.No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{30} (%)	K (min^{-1})	Correlation coefficient values	
						Zero Order	First order
1	F_1	21.9	72.7	30.55	0.0317	0.9724	0.9814
2	F_2	18.7	62.1	34.29	0.0371	0.9582	0.9774
3	F_3	16.3	54.1	37.24	0.0426	0.9463	0.9704

Statistical treatment for dissolution efficiencies of Olmesartan medoxomil spherical agglomerates prepared with β-cyclodextrin in different ratios

Table No:-7

Trial	Dissolution efficiencies (%) (DE_{30})			ANOVA Parameters		
	F_1	F_2	F_3	Calculated value (F)	Degree of freedom	Significance
1	30.14	34.11	37.18	445.88	2,6	P<0.05
2	30.67	34.53	37.48			
3	30.84	34.23	37.06			

Evaluation of micromeritic properties of the blend[16]

a) Bulk density

Blend was weighed and transferred to a measuring cylinder. Then bulk volume was noted. Bulk density was calculated by using the following formula

$$\text{Bulk density} = \frac{Massofthepowder}{Bulkvolume}$$

b) Tapped density: Blend was weighed, transferred to a measuring cylinder and subjected to 100 tapings. Then volume was noted as tapped volume. Tapped density was measured by using the following formula

$$\text{Tapped density} = \frac{Massofthepowder}{Tappedvolume}$$

c) Carr's index

Carr's index was calculated by using the following formula

$$\text{Carr's index} = \frac{Tappeddensity - Bulkdensity}{Tappeddensity} \text{ X } 100$$

d) Hausner's ratio

Hausner's ratio was calculated by using the following formula

$$\text{Hausner's ratio} = \frac{Tappeddensity}{Bulkdensity}$$

e) Angle of repose

Required quantity of blend was taken and poured into a hollow cylinder which was placed on a graph sheet. Then the cylinder was slowly lifted. Then height and diameter of the heap formed were noted down. The angle of repose (θ) was calculated by the formula

$$\text{Angle of repose, } \theta = \text{Tan}^{-1}\frac{h}{r}$$

Micrometric properties for formulation blends of Olmesartan Medoxomil Orodispersible Tablets prepared with co processed superdisintegrants

Table No:-8

Formulation code	Bulk density (gm/cm^3)	Tapped Density gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (°)
F_{16}	0.453	0.544	16.72	1.20	28.63
F_{17}	0.475	0.564	15.78	1.19	27.11
F_{18}	0.441	0.517	14.70	1.18	25.12

Preparation of Olmesartan Medoxomil Orodispersible Tablets containing superdisintegrants: Olmesartan medoxomil containing orodispersible tablets were prepared by direct compression process.[87] All the ingredients (shown in Table No:-24) were properly mixed and passed through mesh no. 80. The resulting blend was lubricated with magnesium stearate and talc and compressed into tablets using the Cadmach sixteen stationary punching (round shaped, 7mm thick) machine.

Composition of Olmesartan Medoxomil Orodispersible Tablets prepared with superdisintegrants

Table No:-9

Ingredients	F_{13}	F_{14}	F_{15}
Olmesartan Medoxomil agglomerates	40	40	40
Sodium Starch Glycolate(SSG)	10	--	--
Croscarmalose sodium	--	10	--
Crospovidone	--	--	10
Manitol	70	70	70
Avicel pH 102	76	76	76
Talc	2	2	2
Mg streate	2	2	2
Total weight	200	200	200

In-vitro dissolution data of Olmesartan medoxomil Orodispersible tablets prepared with superdisintegrants

Table No:-10

S.No.	Sampling time (min)	Cumulative % of drug dissolved ($\overline{X}$ ± S.D.)		
		F_{13}	F_{14}	F_{15}
1	0	0	0	0
2	5	34.46	35.51	41.44
3	10	42.68	44.43	57.73

4	15	47.26	57.59	76.72
5	20	60.28	66.01	81.51
6	25	73.87	76.08	86.84
7	30	85.45	88.01	91.33
8	35	88.88	91.11	96.54
9	40	91.28	93.70	98.90
10	45	93.87	96.47	--
11	50	96.30	98.39	--
12	55	97.86	--	--
13	60	99.26	--	--

Dissolution profiles of Olmesartan medoxomil Orodispersible tablets prepared with various superdisintegrants

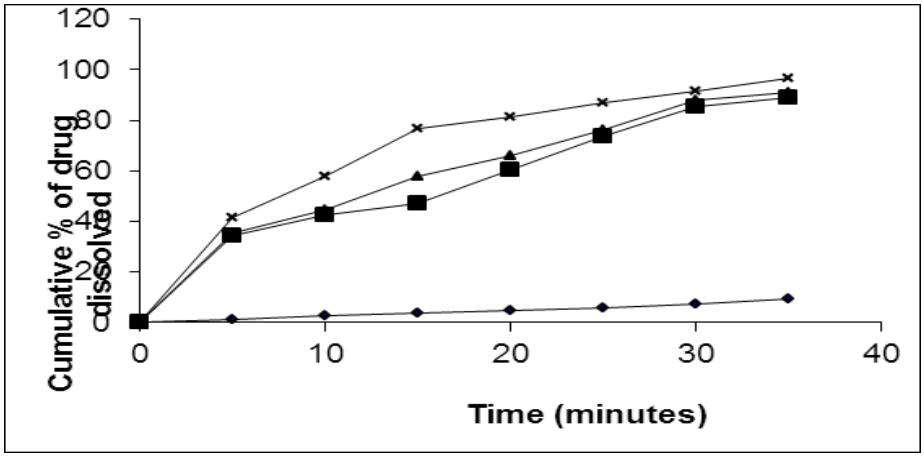

Figure No:-4

(-♦-) Olmesartan medoxomil pure drug

(-■-) Olmesartan medoxomil tablets prepared with sodium starch glycolate

(-▲-)Olmesartan medoxomil tablets prepared with croscarmalosesodium

(-×-) Olmesartan medoxomil tablets prepared with Crospovidone

First order plots of Olmesartan medoxomil Orodispersible tablets prepared with various superdisintegrants

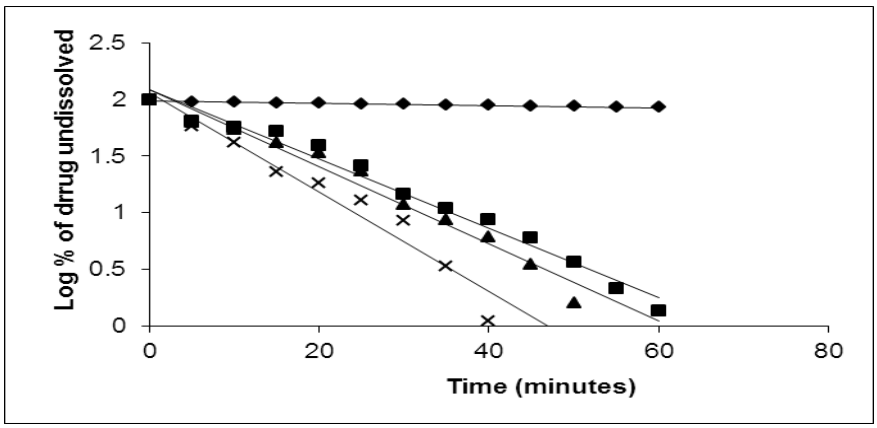

Figure No:-5

(-♦-) Olmesartan medoxomil pure drug

(-■-) Olmesartan medoxomil tablets prepared with sodium starch glycolate

(-▲-)Olmesartan medoxomil tablets prepared with croscarmalosesodium

(-×-) Olmesartan medoxomil tablets prepared with Crospovidone

***In-vitro* dissolution kinetics of Olmesartan medoxomil Orodispersible tablets prepared with various superdisintegrants**

Table No:-10

S.No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{15} (%)	K (min^{-1})	Correlation coefficient values	
						Zero Order	First order
1	F_{13}	10.3	34.1	50.22	0.067	0.8082	0.9734
2	F_{14}	9.6	31.9	54.07	0.072	0.8356	0.9813
3	F_{15}	7.2	29.8	64.99	0.096	0.7582	0.9706

Statistical treatment for dissolution efficiencies of Olmesartan medoxomil Orodispersible tablets prepared with various superdisintegrants

Table No:-11

Trial	Dissolution efficiencies (%) (DE ($_{15}$%)			ANOVA Parameters		
	F_{13}	F_{14}	F_{15}	Calculated value (F)	Degree of freedom	Significance
1	50.14	54.37	64.84	1308.26	2,6	P<0.05
2	50.43	54.53	64.23			
3	50.09	53.31	65.40			

Comparison of dissolution efficiencies of Olmesartan medoxomil Orodispersible tablets prepared with various superdisintegrants

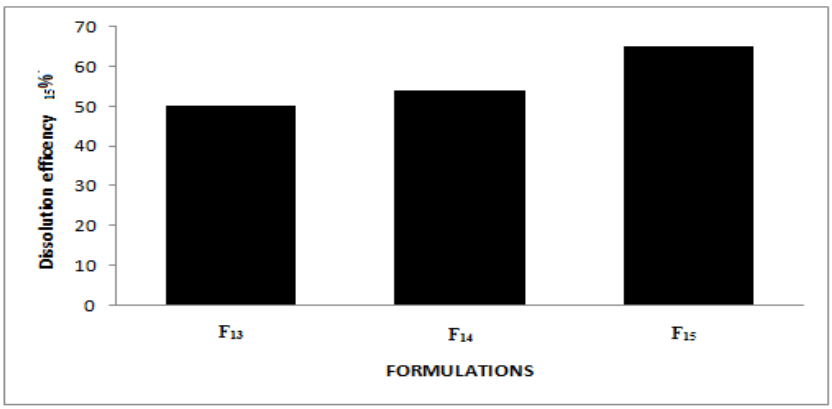

Figure No:-5

Preparation of Co-processed superdisintegrants: Various blends of Croscarmellose sodium and crosspovidone having total weight of 10g were prepared in ratios from 1:1, 1:2, and 1:3 and were added to 6O ml of ethyl alcohol in a 250ml beaker. The contents of the beaker were stirred on a magnetic stirrer. The temperature was maintained between 65ºC and 70ºC, and stirring was continued till the alcohol evaporated.[14] The wet coherent mass was granulated through 60-mesh sieve.

Composition of Olmesartan Medoxomil Orodispersible Tablets prepared with co processed superdisintegrants

Table No:-12

Co-processed superdisintegrants composition ratio	1:1	1:2	1:3
Ingredients	F_{16}	F_{17}	F_{18}
Olmesartan Medoxomil agglomerates	40	40	40
Croscarmalose sodium+ Crospovidone	10	10	10
Manitol	70	70	70
Avicel pH 102	76	76	76
Talc	2	2	2
Mg streate	2	2	2
Total weight	200	200	200

Evaluation of Olmesartan Medoxomil Orodispersible tablets[17-40]

a) Weight variation test

Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight.

b) Disintegration Time

The disintegration time was determined in distilled water at 37±0.5^0 C using disintegration test apparatus[11] USP ED-2L (Electro lab, Mumbai).

c) Friability

Roche Friabilator was used to determine the friability. Pre weighed tablets were placed in Friabilator and rotated at a speed of 25 rpm for 4 minutes or up to 100 revolutions. The tablets are dropped from a distance of 6 inches in each revolution. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated.

d) Hardness

Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning threaded bolts until the tablet fractured. Then the final reading was recorded. The hardness was computed by deducting the initial pressure from the final pressure.

e) Wetting Time

The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a Petri dish with a 10 cm diameter. 10 mL of water-containing amaranth a water soluble dye is added to Petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

f) In vitro dispersion time

Tablet was added to 10 ml of phosphate buffer solution pH 6.8 (pH of saliva) at 37± 0.5°C. Time required for complete dispersion of tablet was measured.

g) Fineness of dispersion

This test was performed by placing two tablets in 100 ml of water and stirring it gently, until the tablets get completely disintegrated. Then the dispersion is passed through a sieve screen with a nominal mesh aperture of 710 μm.

Drug content

Twenty tablets were powdered, and 20 mg equivalent weight of Olmesartan Medoxomil in tablet powder was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 5 ml methanol was added and shaken for 10 min. Then, the volume was made up to 100 ml with 6.8 phosphate buffer. The solution in the volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 258 nm.

Evaluation parameters of Olmesartan Medoxomil Orodispersible Tablets prepared with co processed superdisintegrants

Table No:-13

S.No.	Parameters	F_{16}	F_{17}	F_{18}
1	**Average weight (mg)**	**198+0.2**	**199+0.1**	**200+0.2**
2	**Drug content(%)**	**98.3**	**99.8**	**97.9**

3	**Disintegration time (sec)**	**154**	**141**	**121**
4	**Friability(%)**	**0.24**	**0.45**	**0.43**
5	**Hardness(kg/sqcm)**	**4.2**	**4.2**	**3.8**
6	**Wetting time (sec)**	**131**	**123**	**97**
7	***In-vitro* dispersion time (sec)**	**256**	**214**	**164**
8	**Fineness of dispersion**	**pass**	**pass**	**pass**

i) Dissolution studies

Dissolution studies for Olmesartan Medoxomil Orodispersible tablets were performed in pH 6.8 phosphate buffer using USP dissolution test apparatus (Electrolab, Mumbai, India) with a paddle stirrer. The paddles were allowed to rotate at speed of 100 rpm. The dissolution medium was maintained at a temperature of 37+0.5 ^{O}C and samples were withdrawn at an interval of every 5 min the volume of the withdrawn samples were replaced by fresh dissolution medium in order to kept the volume of the dissolution medium as constant. The withdrawn samples were filtered and absorbance was measured at absorption maxima of 258nm using UV-visible spectrophotometer.

In-vitro dissolution data of Olmesartan Medoxomil Orodispersible Tablets prepared with co processed superdisintegrants
Table No:-14

S.No.	Sampling time (min)	Cumulative % of drug dissolved ($\overline{X}$ ± S.D.)		
		F $_{16}$	**F $_{17}$**	**F $_{18}$**
1	0	0	0	0
2	5	43.71	51.91	63.95
3	10	64.02	75.41	88.39
4	15	77.29	84.56	94.29
5	20	85.75	92.00	99.00
6	25	93.37	98.09	--
7	30	98.07	--	--

Dissolution profiles of Olmesartan Medoxomil Orodispersible Tablets prepared with co processed superdisintegrants

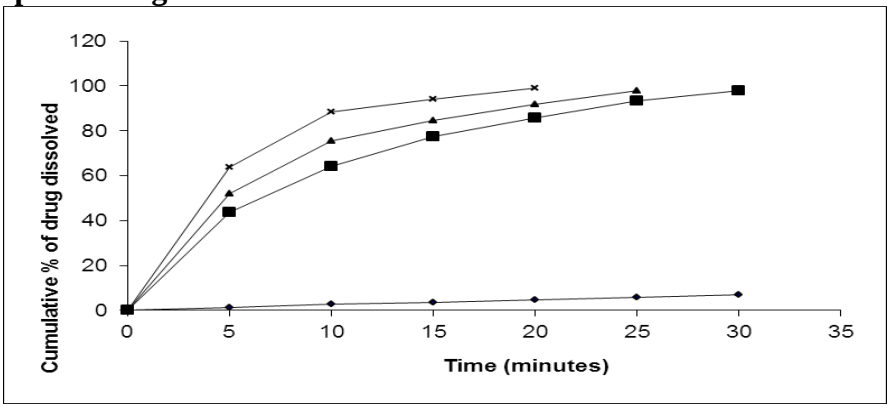

Figure No:-6

(-♦-) Olmesartan medoxomil pure drug

(-■-) Olmesartan medoxomil tablets prepared with crospovidone and croscarmalosesodium in 1:1 ratio by co processing technique

(-▲-)Olmesartan medoxomil tablets prepared with crosspovidone and croscarmalosesodium in 1:2 ratio by co processing technique

(-×-)Olmesartan medoxomil tablets prepared with crosspovidone and croscarmalosesodium in 1:3 ratio by co processing technique

First order plots of Olmesartan Medoxomil Orodispersible Tablets prepared with co-processed superdisintegrants

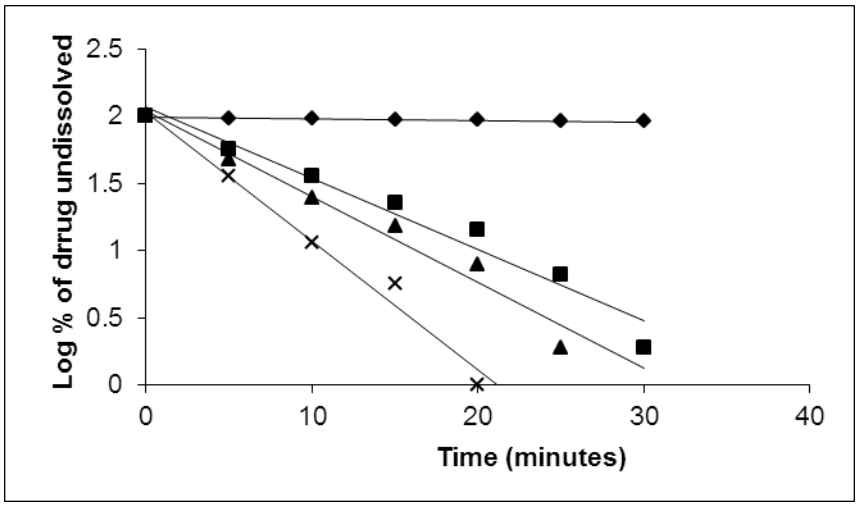

Figure No:-7

(-♦-) Olmesartan medoxomil pure drug

(-■-) Olmesartan medoxomil tablets prepared with crosspovidone and croscarmalosesodium in 1:1 ratio by co processing technique

(-▲-)Olmesartan medoxomil tablets prepared with crosspovidone and croscarmalosesodium in 1:2 ratio by co processing technique

(-×-)Olmesartan medoxomil tablets prepared with crosspovidone and croscarmalosesodium in 1:3 ratio by co processing technique

j) In-vitro dissolution kinetic studies

The drug release data were plotted and tested with zero order (cumulative % drug released Vs time), First order (Log % remained Vs time). The in vitro dissolution kinetic parameters, dissolution rate constants (K^{-1}), correlation coefficient (r), the times (t_{50}) for 50 % drug released (t_{50}), the times for 90 % drug released (t_{90}) and dissolution efficiency [D.E.] were calculated.

In-vitro **dissolution kinetics of Olmesartan medoxomil orodispersible tablets prepared with co-processed superdisintegrants**

Table No:-15

S.No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{15} (%)	K (min^{-1})	Correlation coefficient values	
						Zero Order	First order
1	F_{16}	6.0	20.1	48.80	0.11	0.8493	0.9778
2	F_{17}	4.9	16.2	56.54	0.14	0.8206	0.9825
3	F_{18}	3.2	10.7	66.50	0.21	0.8007	0.9908

Statistical treatment for dissolution efficiencies of Olmesartan medoxomil orodispersible tablets prepared with co processed superdisintegrants

Table No:-16

Trial	Dissolution efficiencies (%) (DE_{15})			ANOVA Parameters		
	F_{16}	F_{17}	F_{18}	Calculated value (F)	Degree of freedom	Significance
1	48.26	56.45	66.56	1486.47	2,6	P<0.05
2	48.79	56.82	66.81			
3	49.35	56.35	66.13			

Comparison for dissolution efficiencies of Olmesartan medoxomil spherical of Olmesartan medoxomil orodispersible tablets prepared with co-processed superdisintegrants

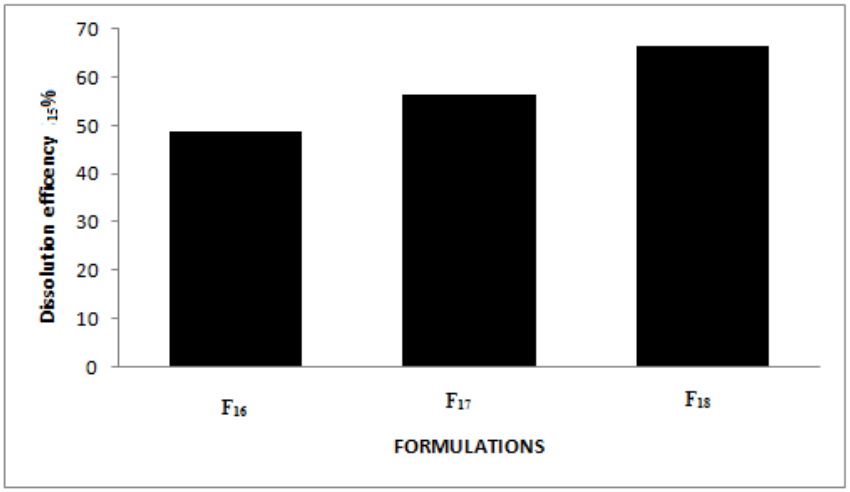

Figure No:-8

Pharmacokinetic evaluation of Olmesartan medoxomil orodispersible tablets[41]

The pharmacokinetic performance of Olmesartan medoxomil orodispersible tablets was studied in a randomized crossover study design in rabbits.[120] Twelve healthy rabbits with a mean age of 10±2 weeks and with a mean body weight of 3±0.2 kg were used. Two groups of rabbits with 6 in each were fasted for 12 hrs prior to study.

The animal dose of Olmesartan medoxomil pure drug and its orodispersible tablets was calculated relevant to human dose. A dose of 0.25 mg/kg of pure Olmesartan medoxomil and 0.25 mg /kg Olmesartan medoxomil equalent orodispersible tablets were administered orally in the form of suspension for two groups of rabbits. The rabbits were restrained in a wooden rabbit holder. The ears of the rabbits were cleaned and the hair was removed with the help of depilatory. Before withdrawal, the ear veins were dilated by swabbing with cotton or by application of warm water. The marginal ear vein of the left ear was punctured with a help of a 24 gauge needle. About 1 ml of blood samples were drawn at 0 (before drug administration), 0.5, 1.0, 2.0, 3.0, 4.0 and 6.0 hrs after pure drug administration and at 0,1, 2, 4, 6, 8, 12, 16, 20, and 24 hrs after administration of Olmesartan medoxomil orodispersible tablets . Blood sample volume was replaced by administration of isotonic saline. . The blood samples were collected in a micro centrifuge tube and centrifuged at 3500 rpm for 10 min. Later the plasma was collected and utilized for estimation of Olmesartan medoxomil concentration.

Estimation of Olmesartan medoxomil in rabbit plasma by HPLC

For the pharmacokinetic studies a method that allows an accurate measurement of low concentration of Olmesartan medoxomil in plasma is required. HPLC method is a sensitive and accurate method that provides a good choice to study the pharmacokinetics of Olmesartan medoxomil *in vivo*.

A summary of the chromatographic conditions used in HPLC are as follows

Chromatographic conditions

Chromatograph	:	Waters 2695 liquid chromatogram
Mobile phase	:	Methanol: Phosphate buffer (80:20 % v/v) pH adjusted to 3 with orthophosphoric acid.
Internal standard	:	Amlodipine besylate
Column	:	Hypersil C_{18} Size - 100×4.60 mm. 5 µm.

Flow rate	:	1 ml/min
Detector	:	UV-Visible detector -2487 Dual absorbance λ detector
Wave length	:	230 nm
Injection volume	:	20 µl
Temperature	:	Ambient
Retention time of the analyte	:	5.883 min
Retention time of the Internal std	:	3.188 min
Total run time	:	8 min
Soft ware	:	Empower 2

$$(AUC)_{0\text{-}\infty} = (AUC)_{0\text{-}24hrs} + C_{24}/K_{el}$$

Determination of mean residence time

The tendency of drugs and metabolites to remain in the body can be assessed by measuring the mean residence time (MRT). The MRT is considered as the statistical moment analogy to the half-life ($t_{1/2}$). It represents the time for 63.2 % of the administered dose to be eliminated. If one considers time course of drug concentration in plasma as statistical distribution curve, it is showed that MRT = AUMC/AUC

Where the AUMC is the area under the "first movement curve" and is obtained from a plot of the product drug concentration in plasma and time versus time from zero to infinity

$$\mathbf{AUMC} = \int_0^\infty ct(t)dt$$

AUC is the area under "zero" moment curve and is obtained by plotting the drug concentration in plasma versus time (c VS t) from zero to infinity.

$$\mathbf{AUC} = \int_0^\infty c(t)dt$$

Plasma Concentration of olmesartan medoximil following pure drug administration and olmesartan medoximil orodispersible tablets administration

Table No:-17

Time (hrs)	Plasma concentration (ng/ml) (Mean ± s.d)	
	Pure drug	olmesartan medoximil orodispersible tablets
0	0	0
0.5	08.51 ±1.86	28.23 ±1.36
1	11.35±1.74	36.44±1.78
1.5	12.51±1.52	42.20±1.56
2	14.61±1.14	45.24±1.24
3	16.75±1.64	49.62±1.12
4	18.81±1.35	54.12±1.65
5	19.62±1.43	61.18±1.67
6	21.93±1.24	68.33±1.85
8	22.76±1.43	62.15±1.72
10	24.90±1.24	57.42±1.22
12	27.72±1.27	49.23 ±1.36
14	24.64±1.36	42.20±1.43
16	21.96±1.53	35.24±1.64
18	18.84±1.32	28.53±1.18
20	15.92±1.21	23.12±1.62
24	12.28±1.39	17.18±1.47

Comparative plasma Concentration -Time Curve of olmesartan medoximil following pure drug and optimized orodispersible tablets administration

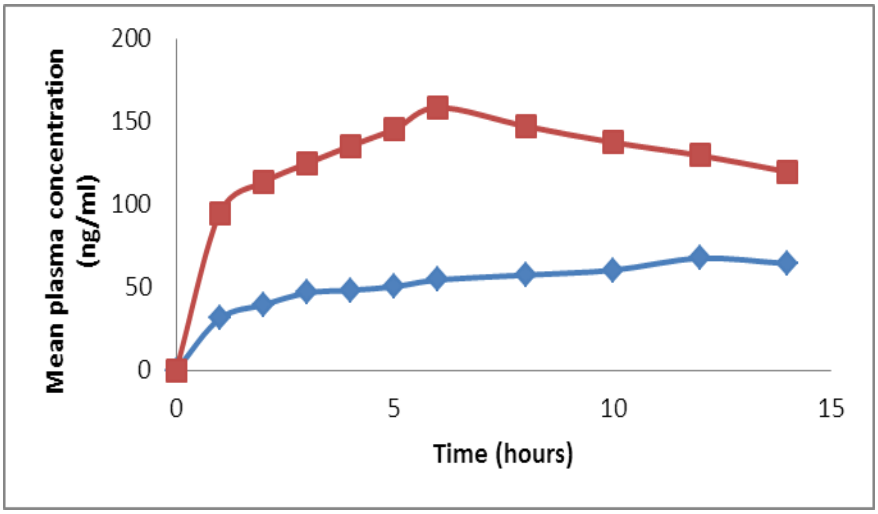

Figure No:-9

(-♦-) plasma Concentration -Time Curve of olmesartan menoxidil following pure drug administration

(-■-) plasma Concentration -Time Curve of olmesartan menoxidil following optimized orodispersible tablets administration

HPLC chromatogram showing olmesartan medoximil and internal standard peaks

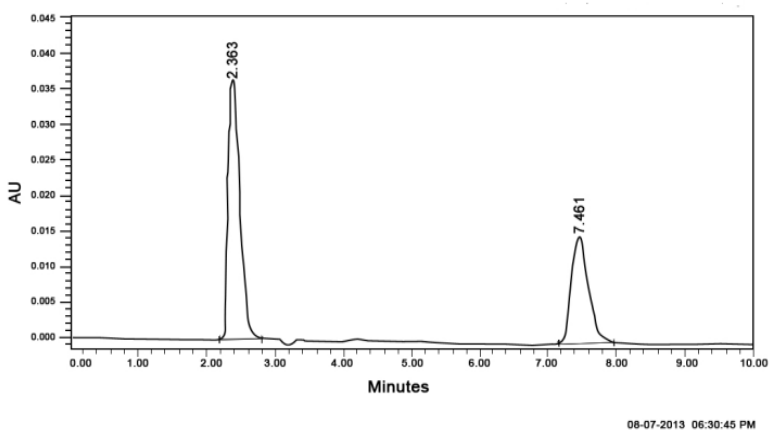

Figure No:-10

	Name	Retention Time (min)	Area (µV*sec)	Height (µV)
1	Amolodipine	2.363	420503	36289
2	Olmesartan	7.461	257535	15073

Statistical Treatment of Pharmacokinetic Parameters (Mean ± S.D.) of olmesartan medoximil obtained with pure drug and optimized orodispersible tablets

Table No:-18

Pharmacokinetic parameter	**Pure Drug**	**Optimized orodispersible tablets**	**Calculated value of 't'**
C_{max} (ng/ml)	27.72 ± 0.31	68.33 ± 0.42	26.70***
$t_{1/2}$ (h)	11.53 ± 0.011	6.09 ± 0.072	40. 75***
K_{el} (h^{-1})	0.58 ± 0.012	0.53 ± 0.014	6.87***
K_a (h^{-1})	1.68 ± 0.01	5.53 ± 0.02	19.67***
$AUC_{0-\infty}$ (ng h/ml)	191 ± 1.43	686.1.±2.07	256.60***
Null hypothesis (H_o): There is no significant difference between the pharmacokinetic parameters of **olmesartan medoximil** obtained with pure drug and optimized **orodispersible tablets**. Table value of't' with 10 DF at the 0.001 level is 4.587.			
Result: H_o is not accepted as the calculated' value more than the table Value of 't' with 10 DF at 0.001 levels of significance. It was therefore concluded that there was significant difference between the pharmacokinetic parameters of obtained with pure drug and optimized **orodispersible tablets**.			

RESULTS AND DISCUSSION

Phase solubility studies of olmesartan medoxomil

Phase solubility studies were done in various pH buffer solutions (pH 1.2 to 7.4), distilled water alone and combination with 0.5%, 1%, 2% SLS solutions. Phase solubility studies of olmesartan medoxomil were given in Table 5.1. From the phase solubility studies it was observed that the drug had more solubility in 6.8 pH buffer. Hence 6.8 pH buffers was selected for the d dissolution medium and standard calibration curve for the estimation of olmesartan medoxomil was carried out in 6.8 pH phosphate buffer. The results are given in Table 5.2 and shown in Fig 5.1. The method obeys Beer's law in the concentration range of 5-25µg /ml. Low RSD values ensured reproducibility of the method. Thus, the method was found to be suitable for the estimation of Olmesartan medoxomil content in various products and *in-vitro* dissolution studies.

Preparation of Olmesartan medoxomil Spherical agglomerates

All spherical agglomerates were obtained by the emulsion solvent diffusion method in which droplets of solvent formed the quasi emulsion. The continuous phase is a liquid in which the drug solution is immiscible. Crystallization occurs inside the droplets because of counter diffusion of solvents through the droplets. The solubility of Olmesartan medoxomil in ethanol, dimethyl sulfoxide and dimethyl formamide is approximately 0.2,20,30 mg/ml respectively.

From the solubility data of Olmesartan medoxomil, the good solvent (N-N, dimethyl formamide), bridging agent (chloroform) and poor solvent (distilled water) were selected for the spherical crystallization process. Chloroform was chosen as bridging liquid because of its excellent wettability with the drug and immiscibility with the dispersion medium (poor solvent). Dimethyl formamide is miscible in any proportion with water and chloroform. If the ternary diagram is envisaged, to select the solvent composition, chloroform and water are like an emulsion in a large area of the diagram. The points on the vertex correspond to a pure liquid; those on the sides correspond to a mixture of only two liquids. Since the presence of three liquids is necessary (good solvent, bridging solvent and poor solvent) for spherical agglomeration, points on the sides of the triangle are excluded. 36 points remain for experiments. Each triangle in the ternary diagram was investigated for the crystallization. The optimal ratio for spherical agglomeration is found in zone .These proportions of N-N,

dimethyl formamide (25%)/water (75%) /chloroform (12.5%) were finally choosen for the study.

Ternary diagram to select the solvent composition

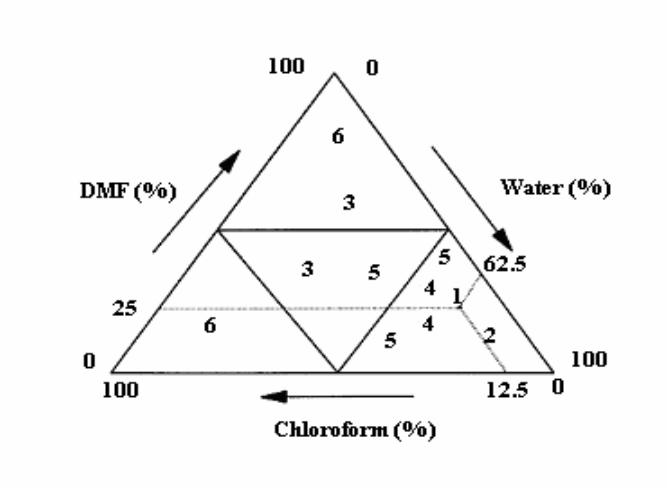

Figure No:-11

The method includes the formation of spherical agglomerates by addition of organic phase containing drug to aqueous solution of the hydrophilic polymer by using a syringe through16# gauge needle. The drug was dissolved in the mixture of good solvent and bridging liquid to form the saturated solution of drug. The solution was poured into distilled water containg surfactants /polymer with stirring rate at 1000 ± 50 rpm by using paddle type of agitator at room temperature.

To optimize Olmesartan medoxomil spherical agglomeration by DMF/water/chloroform system, other process parameters like amount and mode of addition of bridging liquid, stirring speed and time were considered (Table 6.1).

Effect of variables on formulation of spherical agglomerates

Table No:-19

PARAMETERS	OBSERVATION	VARIABLES
Amount of Bridging Liquid	5 ml	No agglomeration
	10 ml	No agglomeration
	12.5 ml	Agglomeration
Agitation Speed	500±50	Clumps
	750±50	Spherical & large
	1000±50	Spherical & small
	1500±50	Irregular shape & small
Time of Stirring	10 minutes	Incomplete agglomerates

	20 minutes	Spherical agglomerates
Mode of Addition of Bridging Liquid	Whole at a time	Crystals of irregular Geometry
	Drop wise	Spherical agglomerates

It was found that the preparations of spherical agglomerates were controlled by two processes, drug-surfactant/polymer complexation and solidification. The combined effect of stirring and stabilizers result in reduction of size and increased hydrophilic characters of the drug. The solidified crystals were dried at room temperature. The manufacturing of a spherical agglomerates implies the creation of additional surface area and hence interface. As the Gibbs free energy change, associated with the formation of additional interface is positive, the spherical agglomerates formed are thermodynamically unstable and will tend to minimize their total energy by agglomeration. Kinetically, the process of agglomeration depends on its activation energy. This activation energy can be influenced by adding stabilizers to the system. A first requirement for a stabilizing system is that it provides wetting of the hydrophobic surfaces of the drug particles.

The practical yield was found satisfactory and ranged from 90.34% to 94.56%. The presence of polymers in spherical agglomerates influenced the particle size of resultant agglomerates. As the concentration of the surfactants/polymers increased, the size of the agglomerates increased. The presence of polymers on the particle surface increases particle–particle interaction, causing faster squeezing out of good solvent to the Surface, resulting in increased particle size. The primary particle size was also increased with an increase in surfactants/polymer content.

Evaluation of spherical agglomerates

Solubility study: The results of solubility study (Table No-10) revealed that the spherical agglomerates with different polymers and stabilizers showed increased solubility compared to the pure drug. This may be due to the improved porosity, decreased primary particle size and partial amorphization of drug in agglomerates. This may also be due to the improved wettability of spherical agglomerates in the presence of polymers and stabilizers.

Drug content: The drug content values were ranged from 92.19 % to 98.18% and are shown in Table No:-10.

Dissolution studies of spherical agglomerates

Olmesartan medoxomil spherical agglomerates prepared with B-cyclodextrin in different ratios

The Olmesartan medoxomil spherical agglomerates prepared with B-cyclodextrin in different ratios exhibited better dissolution rate when compared with plain drug, which could be attributed to deposition of surfactants onto the recrystallized drug surface.

The dissolution data was presented in Table No:-12 and Figure No:-11. The dissolution kinetics was presented in Table No:-13. The dissolution rate followed first-order kinetics (Figure No:-12) as the graphs drawn between log % drug undissolved Vs time were found to be linear. The dissolution rate of Olmesartan medoxomil was found to be effected by the concentration of the surfactants used in the preparation of agglomerates. The *in vitro* dissolution studies of the spherical agglomerates prepared at 1:1(drug: B-cyclodextrin) ratio showed 94.26 % release in 60 minutes. Based on the dissolution rate, the order of drug release from the three formulations was F_3 (1:1) > F_2 (1:0.75)> F_1.(1:0.5).

A statistically significant difference between dissolution efficiencies (DE_{30}) of Olmesartan medoxomil spherical agglomerates prepared with B-cyclodextrin in different ratios was calculated using a one-way analysis of variance (ANOVA). The resulting statistical parameters are shown in Table No:-14 and in Figure 5.4. The P value was found to be less than 0.05, which indicates that there was a significant difference among F_1, F_2, F_3, with respect to dissolution efficiencies (DE_{30}).

Agglomerates prepared with various hydrophilic polymers

Olmesartan medoxomil spherical agglomerates prepared with β -cyclodextrin > Olmesartan medoxomil spherical agglomerates prepared with Hp β-cyclodextrin > Olmesartan medoxomil spherical agglomerates prepared with PVP –K90> Olmesartan medoxomil spherical agglomerates prepared with PVA.Among all the formulations prepared, spherical agglomerates prepared with Olmesartan medoxomil and β-cyclodextrin in 1:1 ratio showed highest drug release in 60 minutes.

β -cyclodextrin > Hp β -cyclodextrin > PVP –K90> PVA

Influence of superdisintegrants on Olmesartan Medoxomil Orodispersible Tablets

To study the influence of superdisintegrants on the performance of Olmesartan Medoxomil Orodispersible Tablets, a set of three formulations (F_{13}, F_{14} and F_{15}) were prepared using

three different superdisintegrants *viz*, Sodium starchglycolate(5%), Croscarmalose sodium(5%), Crospovidone (5%) respectively. The dissolution data was presented in Table No-31 and Figurer No-22. The *In-vitro* dissolution kinetics was presented in Table No-32. The dissolution rate followed first-order kinetics (Figure No-23) as the graphs drawn between log % drug unreleased vs time were found to be linear. The dissolution rate of Olmesartan Medoxomil was found to be effected by nature of the superdisintegrants used in the preparation of tablets. Based on the dissolution rate, superdisintegrants can be rated as,

Crospovidone> Croscarmalose sodium> SSG

The formulation prepared with Crospovidone was offered relatively rapid release of Olmesartan Medoxomil when compared with other superdisintegrants used in this investigation.

A statistically significant difference between dissolution efficiencies (DE_{15}) of Olmesartan medoxomil Orodispersible Tablets prepared with three different superdisintegrants *viz*, Sodium starchglycolate(5%), Croscarmalose sodium(5%), Crospovidone (5%) was calculated using a one-way analysis of variance (ANOVA). The resulting statistical parameters are shown in Table No:-33 and in Figure No- 25. The P value was found to be less than 0.05, which indicates that there was a significant difference among F_{13}, $F_{14,}$ F_{15} with respect to dissolution efficiencies (DE_{15}).

Influence of co processed superdisintegrants on Olmesartan Medoxomil Orodispersible Tablets

To study the influence of co-processed superdisintegrants on performance of Olmesartan Medoxomil Orodispersible Tablets, a set of three formulations (F_{16}, F_{17}, F_{18}) were prepared using co-processed superdisintegrants (Croscarmalose sodium: Crospovidone) in three different ratios 1:1, 1:2, 1:3 respectively. The formulated tablets were subjected to various quality control tests and the results were shown in Table No-30&31.All the tablets complied with the pharmacopoeial standards. The dissolution data was presented in Table No:-31and Figure No:-23. The *In-vitro* dissolution kinetics was presented in Table No-32. The dissolution rate followed first-order kinetics (Figure No:-24) as the graphs drawn between log % drug unreleased vs time were found to be linear. The dissolution rate of Olmesartan Medoxomil was found to be effected by ratio's of co-processed superdisintegrants (Croscarmalose sodium: Crospovidone) used in the preparation of tablets. Based on the dissolution rate, the order of drug release from the three formulations was F_{18}> F_{17}> F_{16}. The

formulation prepared with co-processed superdisintegrants (Croscarmalose sodium: Crospovidone) in 1:3 ratio (F_{18}) was offered relatively rapid release of Olmesartan Medoxomil when compared with other ratios employed in this investigation. The rate of drug release was found to be increased as the concentration of the Crospovidone increases in co-processed superdisintegrants of Croscarmalose sodium: Crospovidone.

A statistically significant difference between dissolution efficiencies (DE_{15}) of Olmesartan medoxomil Orodispersible Tablets prepared with co-processed superdisintegrants (Croscarmalose sodium: Crospovidone) in different ratios was calculated using a one-way analysis of variance (ANOVA). The resulting statistical parameters are shown in Table No:-28 and in Figure No:-25. The P value was found to be less than 0.05, which indicates that there was a significant difference among F_{16}, $F_{17,}$ and F18 with respect to dissolution efficiencies (DE_{15}).

CONCLUSION

Present study concluded that spherical agglomerates prepared by the quasi emulsion solvent diffusion method showed an improvement in the solubility, dissolution rate, compatibility, wettability, flowability and bioavilability.These spherical agglomerates also showed excellent physico-chemical characters as compared with plain drug which indicates that the spherical agglomerates can suitable for directly compressible tablet process.

REFERENCES

1. Kawashima Y, Okumura M, Takenaka H. Spherical crystallization: direct spherical agglomeration of Salicylic acid crystals during crystallization. Science. 1982; 216(4): 1127-28.
2. Ueda M, Nakamura Y, Makita H, Imasato Y, Kawashima Y. Particle design of Enoxacin by spherical crystallization technique II, Characteristics of agglomerated crystals. Chem Pharm Bull. 1991; 39(5):1277-1281.
3. Kawashima Y. Development of spherical crystallization technique and its application to pharmaceutical systems. Arch Pharm. Res. 1984; 7(2): 145-151.
4. Kawashima Y, Ohno H, Takenaka H. Prepartion of spherical matrixes of prolonged release drug from liquid suspension. J. Pharm. Sci. 1981; 70(8): 913-916.
5. Kawashima Y, Furukawa K, Takenaka H. The physicochemical parameters determining the size of agglomerate prepared by the wet spherical agglomeration technique. Powder Technol. 1981; 30: 211.

6. Paradkar AR, Pawar AP, Mahadik KR, Kadam SS. Spherical crystallization: a novel particle design technique. Indian Drugs 1994; 6: 229–233.
7. Patil SV, Sahoo SK. Pharmaceutical overview of spherical crystallization Research Library. Der Pharmacia Lettre, 2010; 2(1): 421-426.
8. Imroz S.M., Shaik Firoz, Chandramouli Y, Chakrapani M. A review on spherical crystallization: a novel particle design technique for direct compression of pharmaceutical powders. 2012; 2(2): 113-121.
9. Highuchi T, Connors KA. Phase solubility techniques. Adv Anal Chem Instrum .1965; 4: 117-120.
10. Bong Sang Lee, Myung Joo Kang, Woo Sik Choi .Solubilized formulation of olmesartan medoxomil for enhancing oral bioavailability. Archives of Pharmacal Research.2009; 32(11): 1629-1635.
11. Mauik Patel, Madhahai Patel, Matvarbhai Patel, Anil Bhandari.Formulation and Assessment of Lipid Based Formulation Of Olmesartan Medoxomil. Int. J. Drug Dev. & Res., 2011; 3(3): 320-327.
12. Thakkar HP, Patel BV, Thakkar SP.Development and characterization of nanosuspensions of olmesartan medoxomil for bioavailability enhancement. J Pharm Bioallied Sci. 2011; 3(3):426 34.
13. Elnawawy TM, Swailem A.M, Ghorab DM, Nour SAk. Solubility enhancement of olmesartan by utilization of solid dispersion and complexation techniques. Int J Nov Drug Deliv Tech. 2012; 2(4): 297-303.
14. Yadav A A., Yadav D S, Karekar P S, Pore Y V, Gajare P. Enhanced solubility and dissolution rate of Olmesartan medoxomil using crystallo-co-agglomeration technique. Der Pharmacia Sinica; 2012; 3(2): 160-164.
15. Yadav V.B, Yadav A.V. Effect of Different Stabilizers and Polymers on Spherical Agglomerates of Gresiofulvine by Emulsion Solvent Diffusion (ESD) System. Int.J. PharmTech Re 2009; 1(2): 149-150.
16. Felodipine by quasi-emulsion solvent diffusion method.Der Pharmacia Sinica 2010; 1 (1): 136-146.
17. Sanjeev Kumar, Pradeep Kumar, Chanderparkash, Shailendra K Singh. Evaluation of Some Novel Techniques For Dissolution Enhancement of Poorly Water Soluble Drug Nimodipine Int.J. PharmTech Res 2010; 2(1): 950-959.
18. Ranjit Dash, Ajit Kumar Acharya, Sanysi Swain, Mayank Barg, Hemant Kumar Choudhary, Khageswar Meher. Formulation and Evaluation of Spherical Crystal of

Etoricoxib. International Journal of Pharmaceutical & Biological Archives 2011; 2(4): 1123-1129.

19. Highuchi T, Connors KA. Phase solubility techniques. Adv Anal Chem Instrum .1965; 4: 117 120.
20. Gorakh J. Dhumal, Durgacharan A. Bhagwat, John I. Disouza. Formulation and Evaluation of Fast Dissolving Buccal Patch of Olmesartan Medoxomil. Asian Journal of Biomedical and Pharmaceutical Sciences, 2013, 3(21): 51-55.
21. Sanjeev Kumar , Pradeep Kumar, Chanderparkash, Shailendra K Singh. Evaluation of Some Novel Techniques For Dissolution Enhancement of Poorly Water Soluble Drug Nimodipine.International Journal of PharmTech Research. 2010; 2(1): 950-959.
22. Mauik Patel, Madhahai Patel, Matvarbhai Patel, Anil Bhandari. Formulation And Assessment Of Lipid Based Formulation Of Olmesartan Medoxomil. Int. J. Drug Dev. & Res., 2011; 3(3): 320-327.
23. Manish R. Bhise, Sandip B. Sapkal, Mahesh B. Narkhede, Gautam D. M. Formulation and evaluation of intraorally fast dissolving tablet of olmesartan medoxomil. Der Pharmacia Lettre, 2013; 5(1): 232-237.
24. Ashwini A. Y, Dhanashri S. Y, Poonam S. K, Yogesh V. P,Pankaj G. Enhanced solubility and dissolution rate of Olmesartan medoxomil using crystallo-co-agglomeration technique. Der Pharmacia Sinica, 2012, 3(2): 160-169.
25. Sano A, Kuriki T, Kawashima Y, Takeuchi H, NiwaT.and Hino T., Particle design of Tolbutamine by spherical crystallization technique. V. Improvement dissolution and bioavailability of direct compressed tablets prepared using Tolbutamine agglomerated crystals.Chem Pharm Bull, 1990; 40(11): 3030-3035.
26. Sai Kishore.V. Gopala krishna murthy T. E., Pavan Kumar A,. Madhu Babu K. Formulation of Valsartan Fast Dissolving Tablets Using Novel Co Processed Superdisintegrants, Research J. Pharma. Dosage Forms and Tech. 2012; 4(1): 52-55.
27. Pandey B K, Mallik Santanu, Ahmad Shamim . Co-processing of superdisintegrants for drug release of taste masked Drotaverine HCL. Novel Science International Journal of Pharmaceutical Science 2012; 1(11-12): 758 -763.
28. Battue S K, Repay M.A, Maunder S, Rio M Y. Formulation and evaluation of rapidly disintegrating tablet Fenoverine tablets: Effect of superdisintegrants. Drug.Dev. Ind. Pharm 2007; 33: 1225-1232.

29. SaiKishore.V. Gopal Krishna murthy T. E., Pavan Kumar A, Satyanaryana J. Formulation and Evaluation of valsartan fast dissolving tablets, Research J.Pharm. And Tech 2011; 4(5): 454-456.
30. Chirag Raval, Neha joshi, Jitendra patel, Upadhya .U.M. Enhanced oral bioavilability of Olmesartan by using novel solid self emulsifying drug delivery systems.International Journal of advanced pharmaceutics. 2012; 2(2): 82-92.
31. Sasidhar RLC, Vidhyadhar S,Maheswari GV, Deepthi B, Srinivasa babu P.Solubility and dissolution rate of Olmesartan medoxomil by complexation and development of mouth dissolving tablets. Advances in Biological Research 7 (2): 32-41, 2013.
32. Abdelbary G, Eouani C, Prinderre P, Joachim J, Reynier JP, Piccerelle P. Determination of the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. Int J Pharm. 2005; 292(1-2): 29–41.
33. Sehgal Prateek, Gupta Ramdayal, Ashwani Chaturvedi, Gulati Ashwini, Singh Umesh Kumar. Fast dissolving Irbesartan tablets containing solid dispersions of Irbesartan. Novel Science International Journal of Pharmaceutical Science 2012; 1(6): 279-286.
34. Highuchi T, Connors KA. Phase solubility techniques. Adv Anal Chem Instrum .1965; 4: 117-120.
35. Mirzayeh Fashami F, Dorri A, Foroutan S, Bolourchian N. Dissolution rate enhancement of Irbesartan using solid dispersion with PEGs. Research in Pharmaceutical Sciences, 2012; 7(5): 327-332.
36. Chowdary K P R, Ravi Sankar P, Mahaboob Ali S, Ramesh Babu Ch. A Factorial Study on the enhancement of dissolution rate of irbesartan by solid dispersion in starch phosphate and gelucire. Pharmacie Globale (ijcp) 2012; 8(04): 1-4.
37. Anand Kumar M, Santhosh P, Karnaker Reddy T, Prasanna Lakshmi A. Development, Evaluation and Charecterization of surface solid dispersion for solubility and dissolution enhancement of Irbesartan. Int. J. Drug Dev. & Res 2012; 4(1): 263-273.
38. Sano A, Kuriki T, Handa T, Takeuchi H, Kawashima Y., Particle design of Tolbutamine in the presence of soluble polymer or surfactant by the spherical crystallization technique: improvement of dissolution rate. J Pharm Sci, 1987; 76: 471-474.
39. Garima Chawla, Arvind K. Banal. Improved dissolution of a poorly water soluble drug in solid dispersions with polymeric and non-polymeric hydrophilic additives. Acta Pharm. 2008; 58: 257–274.

40. Nakamura H, Inoue T, Arakawa N, Shimizu Y, Yoshigae Y, Fujimori I, et al. Pharmacological and pharmacokinetic study of olmesartan medoxomil in animal diabetic retinopathy models. Eur J Pharmacol 2005; 512: 239.