Formulation, Solid State Characterization and Enhancement of Dissolution Rate of Olmesartan Medoxomil by Polyvinyl Alcohol-Polyethylene Glycol Graft Copolymer Based Nanoparticles

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ABSTRACT

The objectives of present investigation were to prepare and evaluate nanoparticles of Olmesartan medoxomil (OLM) by a precipitation method using polyvinyl alcohol-polyethylene glycol graft copolymer (Kollicoat IR) and to investigate the effect of stirring speed & time on particle size. Particles were characterized for drug content, FTIR, zeta potential (ZP), particle size distribution (Dynamic light scattering), differential scanning calorimeter (DSC), powder X-ray diffraction (PXRD), scanning electron microscopy (SEM), solubility, in vitro release and stability studies. All batches showed drug content in range of 93.24 ± 0.96% to 99.91 ± 0.98%, particle size in range of 136.3-188.9 nm. As stirring speed increased particles of reduced size obtained and vice versa. ZP values of formulations were from -2.28 mV to -17.90 mV & comply with requirement of ZP for stability. Solubility results indicated improvement in solubility of formulations. PXRD analysis showed particles were in same crystalline state as raw OLM. Particle exhibited enhanced dissolution compared to raw material due to reduction in particle size, increased surface area & solubility. When formulated in tablets showed improvement in dissolution, compared to marketed formulation, anti solvent precipitation method is promising tool to prepare OLM particles by using Kollicoat IR as a polymer, for enhancement of solubility, dissolution velocity of OLM.

KEY WORDS: Drug nano particles, Anti solvent method, Olmesartan medoxomil, Kollicoat IR, Solubility and Dissolution.

INTRODUCTION

In development of new chemical entities as successful drugs aqueous solubility is a one of the key determinant. For oral absorption new chemical entities are required to possess physicochemical characteristics that results in acceptable absorption, Butnumber of candidates needs physicochemical modification or special formulation technology.[1] Various companies has developed a various technologies and they realized that these are not a functional. Literature reveals various solublization technologiese. g. solubilisation by using surfactants, formulation of molecular complexes, solid dispersions etc. are applied to overcome solubility they are unable to solubilize molecules and suffers from major drawbacks of stability and principle limitations of these approaches is drug needs to possess certain physico-chemical properties. Micro/Nanoparticles

became one option to 'save' molecule for market and overcomes limitations of other technologies.[2]

Particulate delivery systems have become important in experimental pharmaceutics and clinical medicine; it acts as a carrier for small and large molecules. Particulate systems like micro/nanoparticles have been used as physical approach to alter and improve pharmacokinetic, pharmacodynamics properties of various types of drug molecules. The distinction is often made between micro- and nano particles, being particles with dimensions best described in micrometers and nanometers respectively. In micronization particle size reduces to 1-10 micrometer.[3] Drug nano particles are pure solid drug particles with mean diameter below 1000 nm. Katteboinaa, Chandrasekhar and Balaji *et al.* states that "depending on discipline, e.g. in colloidal chemistry particles are only considered as nanoparticles when they are in size below 20 nm. But based on size unit in pharmaceutical area, nanoparticles should be defined as having size below 1000nm".[4]

In case of nanoparticles particle size is reduced to about 100nm there is drastic change in properties of material. The decreased particle size, increases surface area and solubility of drug manifolds and there is a proportionate increase in bioavailability. It increases not only surface area but also saturation solubility. Nano suspension is an alternative approach for formulation is dispersion of drug nanoparticles in liquid media but stability is the problem with dispersed particles.[5]

Many techniques have been used to produce particulate drug delivery system including mechanical commutation,[6] supercritical fluid technique[7] and anti solvent precipitation process.[8] Mechanical commutation methods need high-energy input and show some disadvantages in practice like electrostatic effects, broad particle size distributions.[9] Supercritical fluid technique is attractive methods for size reduction, providing particles with narrow size distribution. But, they also have limitations of low yield and high equipment cost.[10] Anti solvent precipitation process is promising technique to prepare drug particles, which is based on change of super saturation caused by mixing solution and anti solvent. In this method, it requires two solvents that are miscible.[11] Ideally, drug must dissolve in solvent, but not in anti solvent. Precipitation occurs instantaneously by rapid desolvation of drug. Key to producing particles with reduction in size by anti solvent precipitation is to create conditions that favor very rapid particle formation and little particle growth. Technique presents some advantages, in that it is straightforward method, rapid and easy to perform.

Chemically Olmesartan medoxomil is 4-(1-Hydroxy-1-methylethyl)-2-propyl-(1H-tetrazol-5 yl)[1,1'-biphenyl]-4-yl]methyl- 1H-imdiazole-5-carboxylic acid (5-methyl-2-oxo-1,-3- dioxol-4-yl)methyl ester.OLM is angiotensin-II receptor antagonist that is approved for treatment of hypertension. It dose dependently reduces blood pressure through arterial vasodilation and reduced sodium retention. It is pro drug that is rapidly de-esterified during absorption from gastrointestinal tract to produce active metabolite. Aqueous solubility of OLM is <7.75µg/ml. It is practically insoluble in water and soluble inorganic solvents. Oral bioavailability is only 26% in healthy humans due to low aqueous solubility, unabsorbed drug leads to gastrointestinal side effects such as abdominal pain, dyspepsia, gastroenteritis and nausea.[12]

The objectives of present work were to prepare nano particles by anti solvent precipitation method by using Polyvinyl Alcohol- Polyethylene Glycol Graft Copolymer (Kolicoat IR), characterize prepared particles for drug content uniformity, scanning electron microscopy, particle size distribution by (dynamic light scattering),zeta potential, X-ray powder diffraction study, differential scanning calorimetry, drug interaction studies by Fourier transform infrared spectroscopy, Solubility, *in-vitro* release study. To incorporate nanoparticles in tablets and evaluation of tablets, compare *in-vitro* release study of prepared tablets with marketed formulation and evaluate particles for stability.

MATERIALS AND METHODS

Materials

Olmesartan Medoxomil was a gift sample from Emcure Pharmaceuticals Ltd, Pune. Kollicoat IR were kind gift from Lupin Pharmaceuticals Ltd, Pune, Lactose monohydrate, Microcrystalline cellulose(MCC, Avicel pH-102), Cross carmellose sodium (Ac-Di-Sol), Magnesium stearate, Talc, were Pharma grade and obtained from Emcure Pharmaceuticals Ltd, Pune. Ethanol was Laboratory grade and obtained commercially from Oasis Alcohol Pvt Ltd, Tasavade. Marketed formulations of Olmesartan Medoxomil tablets were purchased from local drug store in karadcity after checking their manufacturing, production and expiry date. All other reagents were of analytical grade.

Preparation of Nanoparticles;

Experimental process for preparation of OLM particles;in short, ethanol and water were used as solvent and anti solvent of OLM respectively. Raw OLM was dissolved in ethanol and solution was filtered through membrane filter with pore size of 0.45 µm to remove

possible particulate impurities. Kollicoat IR added into 10 mL of water, used as initial antisolvent.OLM ethanol solution was added drop wise in water with vigorous stirring speed of 1500 rpm, by using magnetic stirrer (Remi Equipment's Ltd. MLH. India). Immediately particles precipitated from anti solvent and a milk-like suspension was formed spontaneously. After stirring for 5 min, suspension was filtered through membrane filter (0.45 μm), residue was dried in hot air oven (Dolphin India.) at 60°C for 1 day. Prepared formulations were stored at ambient conditions until further use. Composition of drug particles is shown in Table 1.

Characterization of nanoparticles
Micromeritic properties

The sample of OLM and obtained particles of OLM was evaluated for flow properties like angle of repose, bulk density (Make- Electrolab, TDT- 06P, Mumbai.) and tapped density, Carr's index, hausner's ratio.

Solubility analysis in different solvents

Solubility studies of OLM and prepared OLM particles were carried out according to method reported by [Higuchi and Connors].Excess quantity of OLM wastransferred in 20 mL capacity conical flask containing 10ml (water, 0.1 N Hcl, Citrate buffer, Phosphate buffer pH 5.8 and 6.8) covered with aluminum foil, sonicated (Dolphin India) for 30 min. The flasks were shaken on rotary orbital shaker for 24 hrs. Flask was removed and stabilized for 1 hr. Content of each flask was then filtered through Whatmanfilter paper (No. 41). Filtrate was diluted and assayed spectrophotometricaly (Shimadzu Corporation, Japan) at 257nm. Solubility was determined in triplicate (n=3)

Study of effect of variables on particle size
Effect of stirring time

Stirring time was usually important factor to influence on particle size in anti solvent precipitation process. Relationship between particle size and stirring time was studied during formulation of drug particles. Formulations were kept for different stirring time (5, 10, 15min) and particle size of each formulation was examined by using scanning electron microscopy (JEOL, JSM 50A, Tokyo, Japan.)

Effect of polymer concentration

Effect of polymer concentration (Kollicoat IR) on particle size was investigated by preparing drug particles with increasing order of their concentration and evaluated for particle size by using scanning electron microscopy (JEOL, JSM 50A, Tokyo, Japan.)

Determination of Particle Size and particle size distribution (PSD)

Particle size and PSD of particles were determined by dynamic light scattering (NICOMP 380ZLS PSS NICOMP Particle sizing systems Santa Barbara, California USA.) Sample were diluted with three times of water and sonicated to create a homogeneous suspension this diluted suspension was added to sample cell (quartz cuvettes) and put into sample holder unit measurement was carried out in triplicate.

Zeta Potential Analysis

Zeta potential of particles was determined by dynamic light scattering (NICOMP 380ZLS PSS NICOMP Particle sizing systems Santa Barbara, California USA.) Samples were diluted with three times of water to get a homogeneous suspension, this diluted suspension was added into specialized zeta (electrophoretic cell) and put into sample holder unit were an electric field was applied. Measurement was carried out in triplicate.

Drug content determination

Drug content of particles were determined by weighing 10 mg particles from each formulation, transferred it into volumetric flask and added 100 ml of phosphate buffer pH 6.8. Resultant solution was sonicated for 10 min and filtered through Whatmanns filter paper (No. 41). Suitable volume of filtrate was diluted with sufficient quantity of phosphate buffer pH 6.8. Absorbance was measured at 257 nm. Content of OLM was calculated. Sample was analyzed in triplicate. Drug content was calculated for all batches using equation as follows:

$$\text{Drug Content} = O_{act}/O_{ss} \times 100$$

O_{act}: Actual Olmesartan medoxomil content in weight quantity of particles.

O_{ss}: Theoretical amount of olmesartan medoxomil particles.

Drug- Excipients Compatibility Studies (FTIR studies)

FTIR spectra of Olmesartan medoxomil and physical mixture (OLM: Kollicoat IR) and formulation F4 was obtained by using ShimadzuFTIR-8400S spectrophotometer with IR solution software (Shimadzu). Samples were dried under vacuum in order to remove influence of residual moisture. Samples prepared by grinding small amount of sample and corresponding amount of potassium bromide (1:100) in agate mortar and pressed into self-supporting disks. Data were collected over a spectral region from 4500 to 400 cm^{-1}with resolution of 4cm^{1}and 45 scans.

Powder X-ray diffraction

Crystalline state evaluation of pure OLM, Kollicoat IR and formulation was done by using Powder X-Ray Diffraction. PXRD diffractograms of samples were analyzed using an X-ray Diffractometer (D2 Phaser, Bruker.) with Cu–Kα radiation at wavelength of 1.542 Å, generated at 30 mA current, and 40 kV voltages. Samples were analyzed in 2θ range from 5° to 50° using step size of 0.02°.

Differential scanning calorimetry

Thermal properties of powder were investigated with Perkin-Elmer DSC-4 DSC. Amount of product to be analyzed shall range from 4 to 7 mg and placed in perforated aluminum sealed 50 μl pans. Heat runs for sample was set from 50-300^{0}C at scanning rate of 10^{0}C/min, an inert environment was maintained under dry nitrogen flow (100 ml/min). The apparatus was calibrated using pure metal like Indium with known melting points and heat of fusion.

Scanning electron microscopy

Particle morphology was observed using SEM (JEOL, JSM 50A, Tokyo, Japan.) Appropriate amount of OLM powder or glass slide with small drop of the suspension, were fixed on an SEM stub using double-sided adhesive tape and coated with Au at 50mA for 6 min through sputter-coater (KYKY SBC-12, Beijing, China). SEM with secondary electron detector was used to obtain digital images of samples at an accelerating voltage of 10 kV.

In vitro dissolution Study

In vitro dissolution studies were carried out for pure OLM & all formulations by using USP type II apparatus (VDA 6D USP STANDARDS VEEGO.) 40 mg of pure OLM and equivalent amount of OLM particles were used for dissolution studies. 900 ml of Phosphate buffer pH 6.8 was used as dissolution medium maintained at 37 ± 0.5°C and stirred at 50 rpm. 5 mL of aliquot were withdrawn at predetermined intervals &filtered using-Whitman filter paper (No. 41). An equal volume of dissolution medium was replaced after each withdrawal to maintain sink condition, dilutions were made with phosphate buffer pH 6.8 &samples were analyzed by UV spectro photometricaly at 257 nm against phosphate buffer pH 6.8.Cumulative % of drug released was calculated & plotted against function of time.Each test was performed in triplicate (n= 3).

Development of Tablet dosage form
Preparation of powder blends for tablets

Powder blend for tablets was prepared using drug particles (equivalent to 40 mg), Lactose monohydrate used as diluent, microcrystalline Cellulose (MCC, Avicel PH-102) as a diluents and disintegrant, Cross-carmellose Sodium (Ac-Di-Sol) acts as a super disintegrant. All above ingredients were dry blended for 20 min, followed by addition of magnesium stearate (lubricant). Mixtures were then further blended for 10 min.

Formulation of tablets

Composition of tablets is shown in Table 4. Direct compression method was used to prepare tablets. Resultant powder blend of OLM, Lactose monohydrate, Microcrystalline Cellulose (MCC, Avicel PH-102), Cross-carmellose Sodium (Ac-Di-Sol) was manually compressed using KBr hydraulic press (Model M-15.Technosearch instruments, India.) at a pressure of 1 ton, with 8mm punch and die to obtain tablets.

Evaluation of tablets

The prepared tablets were evaluated for official and unofficial evaluation parameters like thickness, hardness, weight variation and friability were measured. Thickness of tablets were determined byusing Vernier caliper (Rajesh chemicals, Mumbai) and hardness by using Pfizer hardness tester. Weight Variation was calculated by selecting twenty tablets randomly. Tablets were weighed individually and average weight was calculated. Friability was calculated as % weightloss of 6 tablets after 100 rotations using friability test apparatus (Roche) Each test was per formed in triplicate (n=3).[13]

Comparison of *In vitro* dissolution profile of prepared tablets (OLM particles) and marketed formulation (olsertain™ 40)

In vitro dissolution studies were carried out for tablets (OLM Nanoparticles of Optimized batch F4) and marketed formulationaccording to method reported in for nanoparticles.

Stability study

Stability study was performed to determine change in physical characteristics like colour, drug content, dissolution behaviour, on storage at room temperature for 3 months. Every month sample was withdrawn and evaluated.

RESULTS AND DISCUSSION

Micromeritic properties

Flow ability of Olmesartan medoxomil was good reflected by values of angle of repose, Carr's index and Hausner's ratio, bulk density, tapped density.The angle of repose of OLM was found to be 33.16 ± 0.83^0 categorized as good flowing. Bulk and tapped density was found to be 0.4169 gm/cm^3, 0.4761gm/cm^3 respectively. Hausner's ratio and Carr's index was found to be 1.14 and 12.4343(%) respectively indicated that OLM has good flow properties.Angle of repose of the formulation F1, F2, F3, F4 was found to be 30.61,29.74,28.92,28.65^0 respectively. Bulk and tapped density of formulation F1, F2, F3, F4 was found to be 0.4201,0.4110,0.4000,0.4347 gm/cm^3 and 0.4663, 0.4545, 0.4347, 0.4505 gm/cm^3 respectively. Hausner's ratio and Carr's index of formulation F1, F2, F3, F4 was found to be 1.109, 1.105, 1.08, 1.03 and 9.9077, 9.570, 7.9825, 3.5072 (%) respectively. It indicated significant reduction in values of angle of repose and Carr's index of particles compared to original drug. OLM had significantly higher angle of repose in comparison to particles which might be due to irregular shape of pure OLM and put barrier in uniform flow particles from funnel. The perfect shape and larger sizeof particles decreased interparticle friction and it could be suggested as one of the reason for easy and uniform flowof particles leading to excellent flow ability of OLM particles.[13]

Solubility analysis in different solvents

Solubility of OLM in various solvents is summarized in Table 2 OLM showed very poor solubility in water and phosphate buffer pH5.8 and high solubility in 0.1N Hcl. The results (Figure 1) indicated that OLM was sparingly soluble in strong acids.Solubility of OLM particles showed drastic improvement in solubility of formulation in water as compared to pure OLM also increased solubility into other solvents. Solubility of formulation was increased due to reduction in particle size, increased in surface area of drug (Noyes–Whitney equation) also; it increased due to Kollicoat IR used as polymer (which is hydrophilic in nature).[14]

Effect of variables on particle size
Effect of stirring time

The relationship between particle size distribution and stirring time is revealed in Figure 2 Formulation was kept for different stirring time. (5, 10,15min) Stirring time is important factor to influence particle size in anti solvent precipitation process. It is evident that there is notable increase in particle size with increase in stirring time. This can be explained by particle growth. When OLM ethanol solution was added into aqueous solution, small particles are formed immediately. During stirring process, formed small particles would collide & aggregate together, which may cause particle growth to larger ones. It can be found that OLM particles own narrow size distribution under shorter stirring time. Therefore, stirring for 5 min was believed as an optimum condition to obtain small particles.[15]

Effect of polymer concentration

Effect of Kollicoat IR concentration on OLM particle size is shown in Figure 3. It was investigated by preparing drug particles with increasing order of their concentration. Results indicated Kollicoat IR molecules were adsorbed onto formed hydrophobic drug particle surface and has good affinity for drug particles and able to provide effective barrier against growth. When 0.25, 0.5, 0.75, 1% (w/v) Kollicoat IR were added into water. Particles size was dramatically decreased with 1% (w/v) concentration of polymer. After that, particles size was not significantly influenced by increasing Kollicoat IR concentration, which indicates that drug particle surface is already sufficiently enveloped by Kollicoat IR molecules. This indicating that Kollicoat IR was plays key role in controlling morphology & size of OLM particles.[16]

Determination of Particle Size and particle size distribution (PSD)

Particle size distribution graphs showed in Figure 4 Particle size of formulations showed in Table 3. Poly dispersivity index is measure of width of distribution. PDI below 0.5 indicating narrow PSD. PDI index of Formulation F1, F2, F3, F4 was (0.452, 0.546, 0.560, 0.299) indicating F4 formulation showed narrow particle size distribution as compared to other formulations.In micronization size ranges from 1-10μm & nanonization size ranges from 1-1000 nm. Results of PSD showed all formulations were found in range of nanometer. Four different formulations were prepared with different concentration of Kollicoat IR. Highest concentration of polymer containing formulation F4 showed smallest particle size. This might be due to use of high concentration of polymer and also may be due to polymer contains hydroxyl groups, which can form hydrogen bonds between drug & polymer. Polymer, presented in aqueous solution absorbed on surface of formed drug particles to inhibit particle growth & controlling size of OLM.[4]

Zeta Potential Analysis

ZP of Formulation was found to be F1, F2, F3, and F4 (-2.28, -9.77, -11.05, -17.90 mV resp.) Kollicoat IR
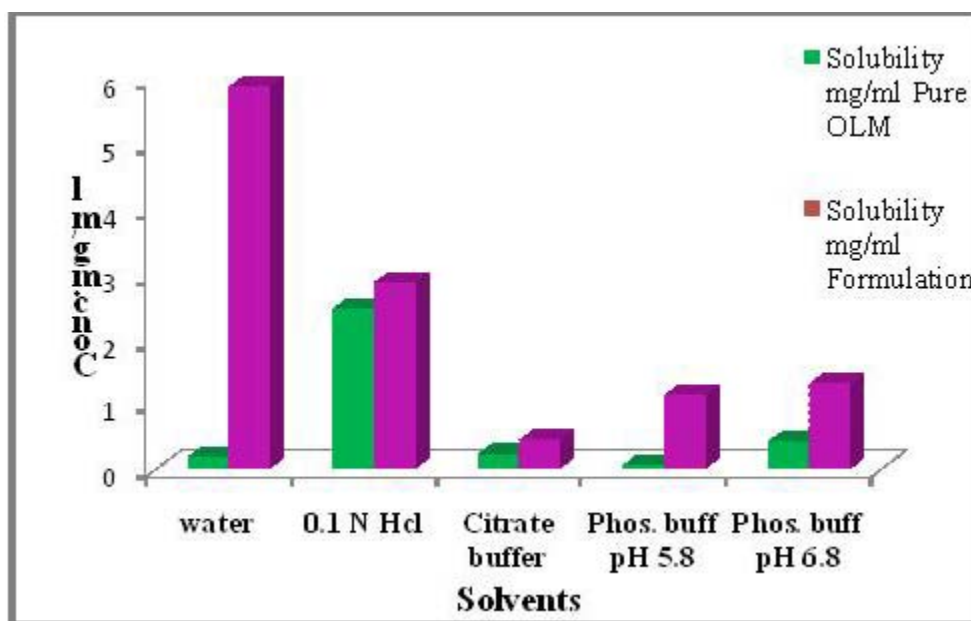
Figure 1: Solubility study of OLM and prepared OLM particles (F4) in different solvents.
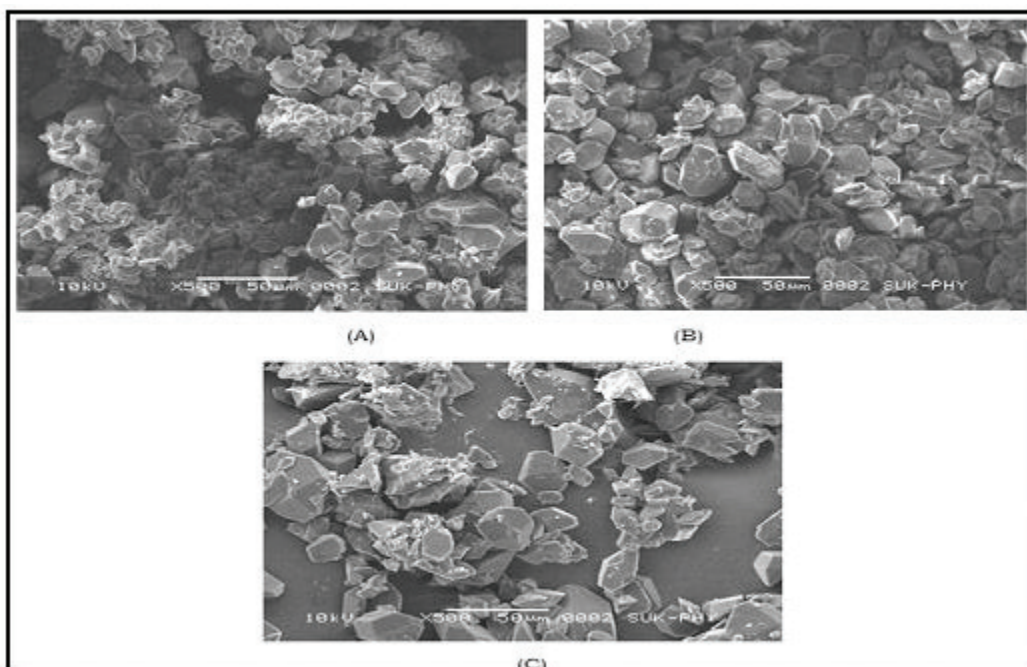

Figure 2: SEM images of OLM particles prepared with different stirring time: (a) 5 min; (b) 1`0 min; (c) 15 min; (OLM ethanol concentration: 30 mg/mL).

used as polymer. It may provide steric stabilization. So, negative zeta potential was attributed for formulations. Formulation F4 complies with requirement of zeta potential for stability.[17-18]

Drug content determination

Drug content of formulation (F1, F2, F3, F4) was found to be 93.24 ± 0.96, 95.53 ± 0.88, 96.52 ± 0.85, 99.91 ± 0.98% respectively. Drug content of OLM was 97.5 % - 102.0 % as per European pharmacopeia. Drug content of Formulation (F4) was found to be (99.91 ± 0.98%) which compiles requirement compared to other formulations. Hence, formulation F4 (1%w/v Kollicoat IR) were selected for tablet preparation.Due to high concentration of Kollicoat IR in Formulation (F4) maximum amount of particles precipitated out from
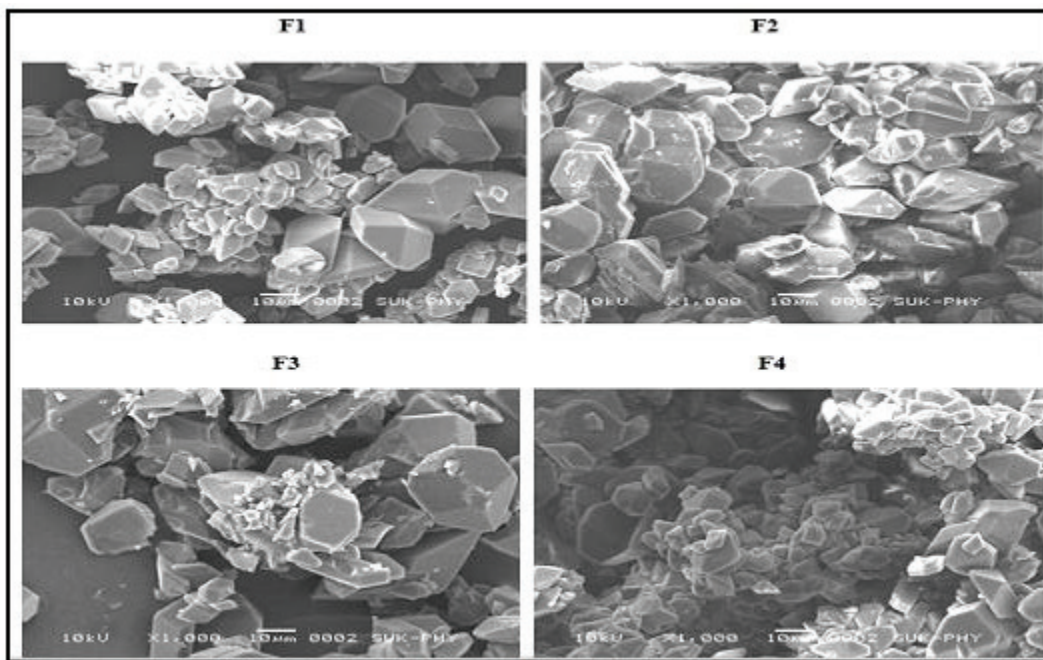
Figure 3: SEM images of OLM particles obtained with different concentration of Kollicoat IR as polymer: (F1) 0.25% (w/v), (F2) 0.5% (w/v), (F3) 0.75% (w/v), (F4) 1% (w/v). (OLM ethanol concentration: 30 mg/mL).
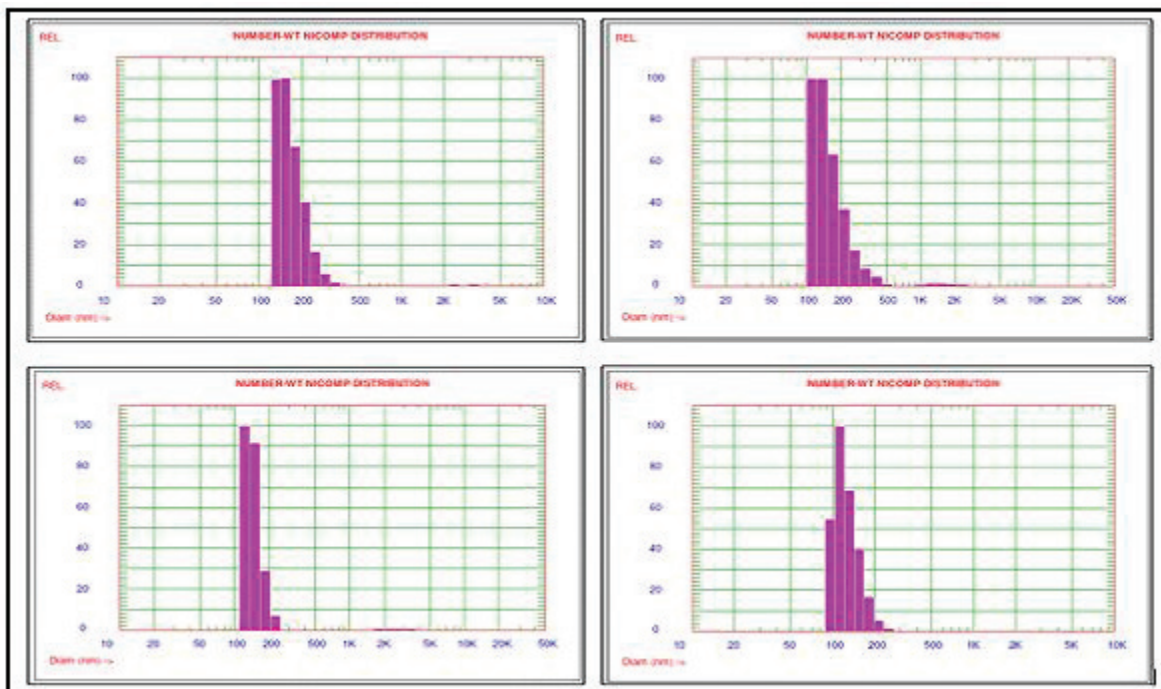

Figure 4: Particle size results of Formulations F1, F2, F3, F4.

solution with coating on surface of particles which increases product content.[19-20]

Drug- Excipient Compatibility Studies (FTIR)

FTIR spectrum of pure olmesartan medoxomil, physical mixture, formulation F4 (Optimized Batch)which are shown in Figure 5 IR spectra of olmesartan medoxomil showed characteristic peaks at 3301 cm-1 (Broad-OH stretch), 1712 cm-1 (C=O ketonic group),2975 cm-1 (C=C-C unsaturation), 1172, 1139 cm-1 (C-N Secondary amine), 1137 cm-1 (C-O-C), 3305 cm-1 (NH-stretch amine), FTIR spectra of physical mixture displayed
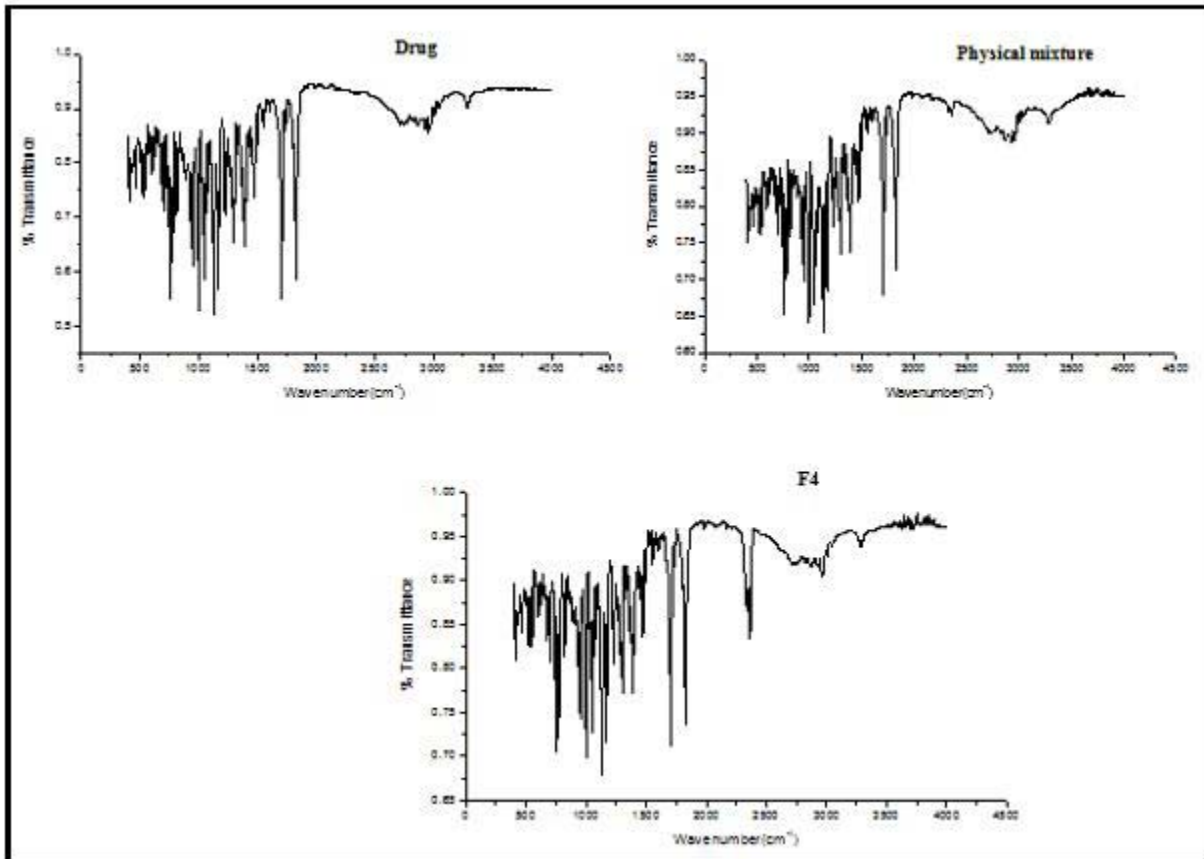
Figure 5: FTIR Spectra of Olmesartan medoxomil, physical mixture, Formulation F4 (Optimized Batch).
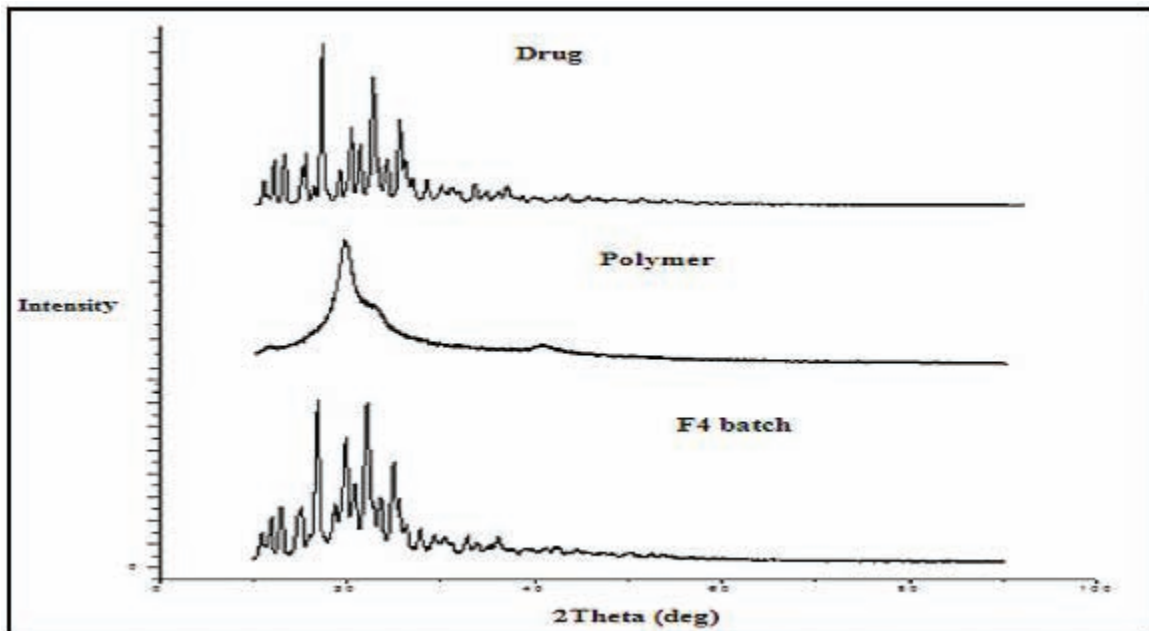

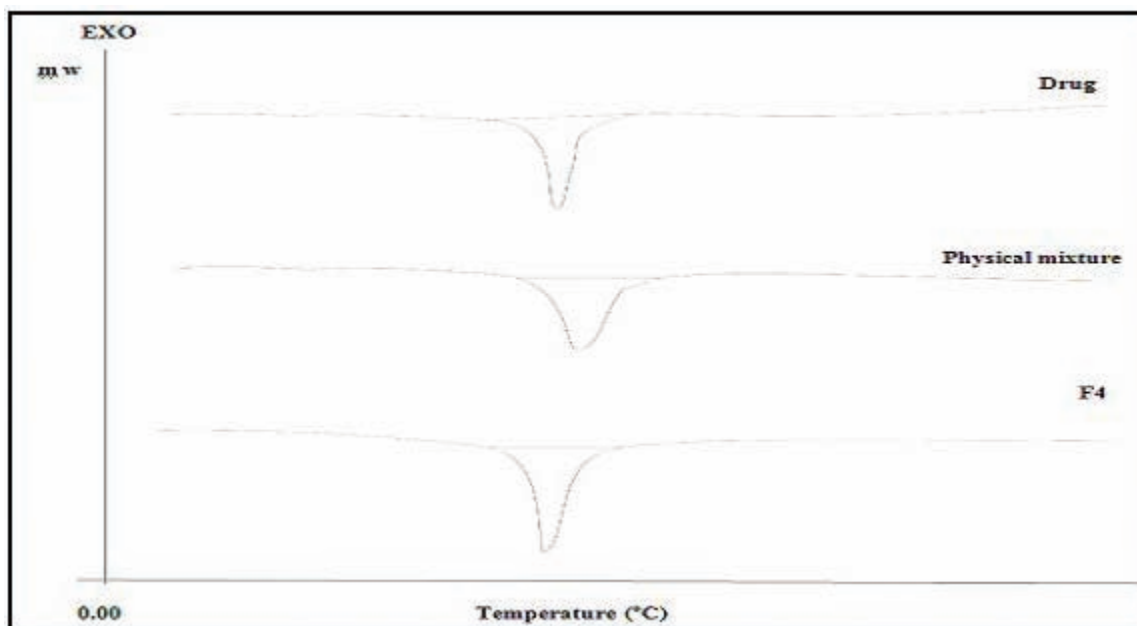**Figure 6: XRPD Pattern of Drug, Polymer, Formulation F4 (Optimized Batch).**

Figure 7: DSC curves of Pure OLM, Physical mixture, Fr (Optimized Batch)
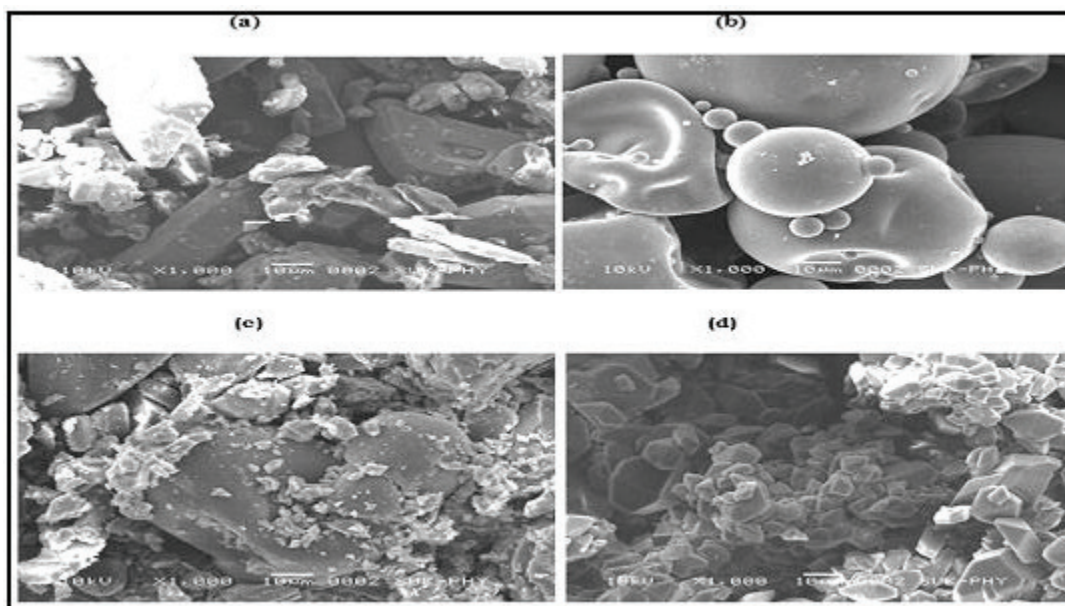

Figure 8: SEM images of (a) Drug (b) Kollicoat IR(c) Physical mixture (OLM: Kollicoat IR) (d) (Formulation F4 (Optimized Batch)

prominent peaks at 3301cm-1 (OH stretch), 1712cm-1 (C=O ketonic group), 1137cm-1 (C-O-C stretch) and 1460cm-1 (=C-H methylelene CH bend),Approx 2880 cm-1 (at high energy CHO). Formulation (F4) showed characteristic band at 3301cm[1](O-H, stretch, broad), 1712cm-1 (C=O), 1137 cm-1 (C-O-C stretch), 2880 cm-1(at high energy CHO), 3305cm-1 (NH-stretch amine). 2453-2376 (Carboxylic acid broad peak).FTIR spectra of physical mixture did not indicate any well-defined interaction between OLM & Kollicoat IR. Therefore it

can be concluded that drug and polymers were compatible with each other. FTIR spectrum of Formulation F4 (Optimized Batch) showed that there were no considerable changes in IR peaks of formulation when compared to pure OLM and no changes have occurred in their chemical structure. The strong interaction between drug and carrier, often leads to identifiable changes in IR profile of the drug but the results of IR spectra indicated an absence of any well-defined interaction between olmesartan medoxomil and Kollicoat IR.
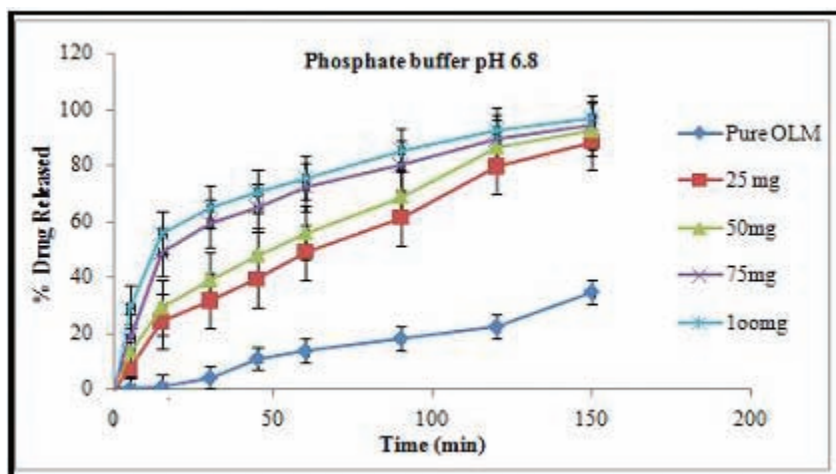
Figure 9: *In-vitro* **Release Profile of all formulations (F1, F2, F3, F4) and Pure OLM in phosphate buffer pH6.8.**
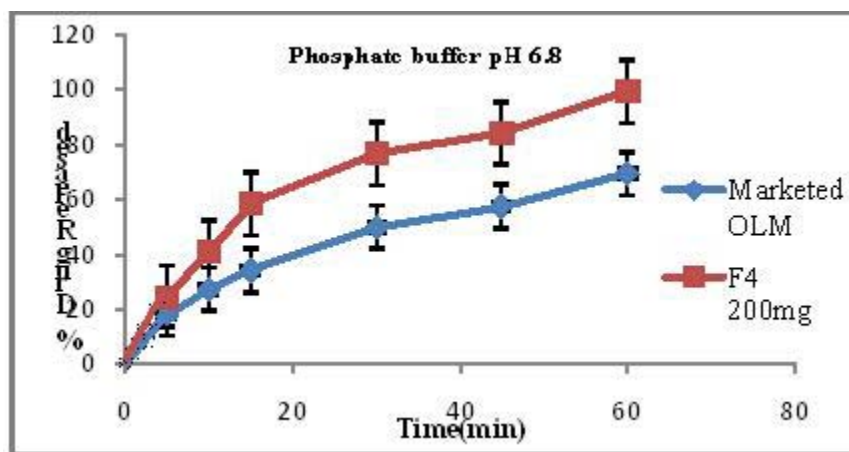

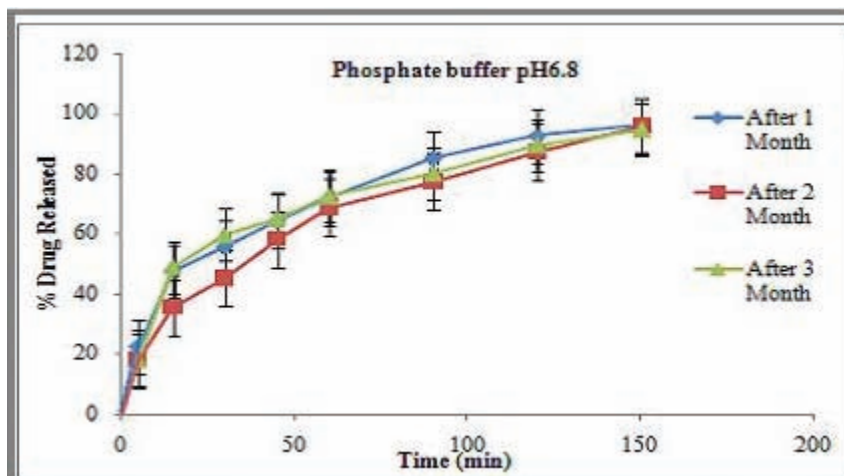**Figure 10:** *In-vitro* **Release Profile of tablets of OLM particles & marketed tablet in phosphate buffer pH6.8.**

Figure 11: *In-vitro* **Release profile of particles (After 1, 2, 3 month) in phosphate buffer pH6.8 (n = 3)**

Table 1: Composition of OLM particles

Batch	Olmesartan Medoxomil	Kollicoat IR	Solvent
F1	300 mg	25 mg	10 ml
F2	300 mg	50 mg	10 ml
F3	300 mg	75 mg	10 ml
F4	300 mg	100 mg	10 ml

Table 2: Solubility study of OLM and prepared OLM particles (F4) in different solvents.

Sr. No.	Solvents	Solubility mg/ml Pure OLM	Solubility mg/ml Formulation (F4)
1	water*	0.19±0.010	5.888±0.833
2	0.1 N HCl*	2.47±0.002	0.8765±0.215
3	Citrate buffer*	0.229±0.006	0.4526±0.405
4	Phos. buff pH 5.8*	0.0642±0.018	1.141±0.186
5	Phos. buff pH 6.8*	0.4237±0.003	1.32±0.405

*Indicates mean ± SD (n = 3)

Table 3: Particle size results of all OLM Formulations

Sr. No.	Formulation Code	Mean Particle size (nm)	PDI
1	F1	188.9	0.452
2	F2	187.6	0.546
3	F3	177.7	0.560
4	F4	136.3	0.299

Table 4: Composition of Tablets

Sr. No.	Ingredient	Quantity/tablet
1	Olmesartan Medoxomil	40 mg
2	Lactose monohydrate	72 mg
3	Microcrystalline cellulose	72 mg
4	Cross carmellose sodium	8 mg
5	Magnesium stearate	4 mg
6	Talc	4 mg
7	Total weight of tablet	200 mg

Powder X-ray diffraction

PXRD used to assess degree of crystallinity of given sample. Raw OLM was highly crystallized and exhibited intense crystalline peaks at 2θ value of 16.78 with high intensity 10606.At same angle F4 (Optimized Batch) showed maximum intensity of about 6372. Kollicoat IR showed 4388 intensity at same 2θ. From results it was found that Pure OLM and Kollicoat IR were in crystalline state. In case of formulation intensity of peaks was reduced, but peak pattern was not changed, drug particles exist in same crystalline state as raw OLM. It has been known that reduction of drug to down size would lead to high-energy state and high disorder, resulting in enhanced dissolution rate and bioavailability[15] PXRD of Pure OLM, Kollicoat IR, F4 (Optimized Batch) shown in Figure 6.

Differential scanning calorimetry

DSC curves of Pure OLM, PM (OLM: Kollicoat IR), F4 (Optimized Batch) shown in Figure 7 DSC analysis has been used to detect all process in which energy was required or produced.DSC curve of pure OLM exhibited sharp endothermic peak at 184.73°c corresponding to melting of drug. While PM showed endothermic peak at 191.45°c.F4 (Optimized Batch) showed endothermic peak at 179.87°c indicated decreases in energy change of melting endotherm, which confirms considerable extent of reduction in crystallinity of drug. DSC results supported XRPD data. This phenomenon could be attributed to reduction in particle size, decreased intensity of particles, which may results into decreased in melting point of particles. Fraction absorbed for drugs with high melting temperatures is limited by dose to greater degree than it is for low melting compounds.[21]

Scanning electron microscopy

SEM images of OLM, Kollicoat IR, PM and F4 Batch which was shown in Figure 8 Photomicrograph of drug indicated that OLM was rod shaped crystalline solid and Kollicoat IR was spherical in shape. Formulation indicated that shape of particles was regular, hexagonal with smooth surface due to coating of polymer onto surface of drug particle, which enable them to flow very easily. Pure OLM is rod cylindrical particles elongated along one axis. OLM precipitated particles were hexagonal particles with faces parallel to growth axis; width and thickness greater than acicular and shorter in length (Prismatic).[22]

In vitro dissolution Study

Plot of % drug released as function of time shown in Figure 9. % drug release of Pure OLM & F1 to F4 was (13.84, 48.92, 55.95, 72.47, and 75.65%) respectively with in period of 60 min. *In vitro* study showed that formulation F4 exhibited better dissolution property than others therefore it was used for further investigations. There was significant difference between dissolution rates of pure drug and particles. This increased in dissolution rate was due to increased surface area of drug due to smaller size. Increased dissolution velocity of OLM particles was in agreement with theory of dissolution by Noyes–Whitney. According to Noyes-Whitney equation,

increased in saturation solubility, decreased in particle size lead to increased dissolution rate. So, formulation of poorly water soluble drugs as nanometer sized drug particles has drastic effect on dissolution rate, solubility, and bioavailability. Bioavailability of OLM was truly dissolution rate limited, so particle size reduction can significantly improve performance of OLM.

Development of Tablets oral dosage form[23]

The formula compositions chosen for tableting are shown in Table 4.

Evaluation of Tablets

The physical propertiessuch as the average weight of the tablet was found to be 200.01 mg. Tablets possessed acceptable mechanical strength with hardness of 4.50 ± 0.25 kg/cm^2. Thickness of tablet was found to be 0.100 ± 0.115 cm and friability was found to be 0.6913 ± 0.25 (%) it was <1% indicating good mechanical strength. All tablet properties meet standards within Pharmacopoeia limits.

Comparison of *In vitro* dissolution profile of prepared tablets (OLM particles) and marketed formulation (olsertain™40)

The Plot of % drug release as function of time shown in Figure 10. % drug release of tablets of OLM particles and marketed tablet was (99.45, 69.5% respectively) within period of 60 min. *In vitro* study showed that tablets of OLM particles exhibited better dissolution than marketed.This increased in dissolution rate was due to presence OLM particles.

Stability study

Optimized batch F_4 was evaluated for stability study. It was conducted for 3 months; every month slightly decreased in drug content of OLM particles &found 97.19 ± 0.39, 97.01 ± 0.61, 96.99 ± 0.43%. All limits were acceptable as per European pharmacopoeia (97.5 % - 102.0%) Dissolution behaviour during stability study shown in Figure 11. Percentage drug release of particles was slightly decreased. Because as time passes particle agglomeration was occurs. Initially formed particles get coagulated to larger once, which reduces surface area &dissolution rate.[24]

CONCLUSION

By using Polyvinyl Alcohol- Polyethylene Glycol Graft Copolymer we can enhance the dissolution rate of BCS class II molecules like OLM. This copolymer can be used for formulation of stable nanoparticles by anti-solvent precipitation technology which is the simple and scalable technique but attention should be given to optimization of stirring speed and stirring time. The prepared nanoparticles showed the improvement in solubility and dissolution rate. When incorporated in a tablet dosage form showed better performance than marketed formulation (olsertain™40).

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SUMMARY

- kollicoat IR can be used for formulation of nanoparticles 2. formulated nanoparticles of OLM showed improved dissolution rate 3. stirring time and speed are important parameters which affects on morphology of particles.

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