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Improved Characteristics of Ofloxacin Agglomerated Crystals using Quassi-Emulsion Solvent Diffusion Method

Narendra Kr. Goyal[1]*, Rishabha Malviya[1], Pramod K Sharma[1], Nitin Sharma[2]

[1]Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University, Greater Noida, U.P., India

[2]Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, Baghpat Crossing, Meerut, India

Abstract: The aim of present investigation was to prepare agglomerated crystals of ofloxacin by Quassi-Emulsion solvent diffusion method (QESDM), for the improvement of powder and tablet characteristics. The agglomerated crystals of ofloxacin were prepared using chloroform, ethanol and distilled water as solvent, bridging agent and poor solvent respectively. Effect of process variables (amount of bridging agent, rotation rate and temperature) were studied for the optimizations of crystals. Agglomerates were characterized for their micrometrics characteristics (bulk density, flowability). Several batches of ofloxacin tablets were prepared by agglomerated crystals, wet granules and physical mixture of drug with exipients. Prepared agglomerates crystals were showing improved micrometrics behavior, which minimized the cost of granulation of ofloxacin. Prepared tablets of agglomerated crystals were better than other tablet batch in terms of hardness, friability, compressibility, disintegration and dissolution time. It can be concluded from results that spherical agglomerated crystallization is an alternative and effective method for favouring direct tabletting to solve the solubility problem of poorly soluble drugs.

Keywords: Ofloxacin, agglomerate, quassi solvent diffusion method, compressibility.

Introduction:

Recently many dosage forms have been discovered for the delivery of pharmaceuticals, but among them, tablet is still having attention for the delivery of pharmaceuticals and biopharmaceuticals. This is due to some basic advantages of tablets, such as simple method of preparation and administration. Several methods have been suggested for tablet formulation. Direct compression of pharmaceutical ingredient is focused with greater impact. Method involves the direct compression of ingredients, required certain physical properties of powder such as flowability, bindability and mechanical strength. Due to this reason there are limited number of tablets are available in the market that can be made by direct tabletting (1). Development of spherical crystals of pharmaceutical active agents for direct compression is now gaining attraction and importance. This is due to the fact that crystal habits such as form, surface, size and particle size distribution may be changed during crystallization process. During the modifications of crystal habits, certain physical properties such as bulk density, flow property, compactibility and dissolution rate of powder are also changed and modified (2). Spherical crystallization can be done by several methods including, spherical agglomeration, Quassi solvent diffusion method (QSDM), ammonia diffusion method and neutralization method. Among them QSDM is commonly used for the preparation of spherical crystals (3). This method involves three solvent system, good

solvent, poor solvent and bridging agent. Pharmaceutical ingredients are dissolved in the good solvent and dispersed in the poor solvent, to make an emulsion (quassi). Poor solvent are diffused in to the emulsion droplets and pharmaceutical ingredients are crystallized in a controlled manner (4).

Ofloxacin (OFX) is freely soluble in acetic acid but slightly soluble in water, methanol, ethanol or acetone. Oral bioavailability of drug is low, due to its poor solubility in water. Powder of drug shows poor flowability and others physicochemical properties necessary for the direct compression (5) (6).

In the present work, an attempt has made to overcome the limitations related to flowability, compressibility, solubility and dissolution rate of OFX by QSDM method for direct compression of tablets. Method involves the preparation of spherical agglomerated crystals with improved physicochemical properties, which are ready for direct compression. Physical characteristics and tablet behaviors of agglomerates were compared with those of OFX powder and its granules. Method is also beneficial in the terms of economy due to the avoidance of others tabletting ingrediences and expensive method (wet granulation).

Materials and Method

Materials: Ofloxacin was obtained as gift sample from Unicure Pharmaceutical Pvt. Ltd, Roorkee. Its purity was confirmed by testing its melting points, solubility study and by examining its IR spectra. All the solvents were pure of laboratory grade and were purchased from Ranchem laboratory. Other ingredients were of pharmaceutical grade and purchased from CDH analytical reagent.

Preparation of Ofloxacin agglomerates: Different solvent for the preparation of agglomerate of drug was selected by following the general rule of Chow and Leung (7). Ofloxacin (1.25gm) was dissolved in the mixture of good solvent chloroform (15ml) and bridging agent ethanol (1ml, 3ml, 5ml) to form the saturated solution of drug. The solution was poured into 80ml of distilled water (poor solvent) with stirring rate at 800, 1000 and 1200 rpm by using paddle type of agitator at room temperature, 50^0C and 70^0C for 30 minutes for the optimization of spherical agglomerate crystals. Optimization of agglomerates was done on the basis of shape of agglomerates and percentage yield. Shape of agglomerates was evaluated by using Phase contrast microscope (OLYMPUS) similarly percentage yield were find out by simple weighting method. After this, the optimized agglomerates were collected by filtration through Whatman filter paper no.42 under the vacuum, washed the crystals with distilled water and placed at 50^0C for drying in hot air oven and stored in desiccators (8, 9).

Preparation of Granules by Wet Granulation Method: All the ingredients were accurately weighted in specified amount (as shown in table-1) and mixed homogeneously. Then wet granules were prepared by wet granulation method using polyvinylpyrollodine as granulating agent and passing them from sieve no # 22. Granules were dried and stored in desiccators.

FT-IR Spectroscopy: Fourier Transform Infrared (FT-IR) spectroscopy was conducted using a Shimadzu FT-IR Spectrophotometer (Shimadzu, Tokyo, Japan) to detect possible polymorphic transition, excipient & solvent interaction during the crystallization & granulation process. Spectrum was recorded in the wavelength region of 4000– 400 cm^{-1}. The procedure consisted of dispersing a sample (drug alone, physical mixture of drug and polymer or spherical agglomerates) in KBr and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained.

Comparison of powder characteristics of conventional OFX, granules and agglomerated crystals:

Particle size analysis: - The morphology and particle size of prepared agglomerate were determined by digital microscope equipped with a 1/3”CCD camera imaging accessory and computer controlled image analysis software. Prepared agglomerates were dispersed on the slide in paraffin oil. A microscopical field was scanned by video camera. The image of the scanned field was analyzed using software.

Particle size distribution: Particle size distribution was carried out using electromagnetic sieve shaker (Electrolab). 50 g of agglomerates were placed on the top sieve of mechanical shaker and by following 200 strokes/min for 10 min, than the amount of fraction of powder retain on individual sieve was determined by weight to calculate the size distribution.

Micromeritic Properties & Flowability: The loose bulk density (LBD) and tapped bulk densities (TBD) were determined by using density apparatus (Serwell, Bangalore, India). The Carr's index (%) and the Hausner's ratio were then calculated by using LBD and TBD. The angle of repose of drug powder and the agglomerates were assessed by fixed funnel method (10-11).

Porosity: Porosity was calculated as follow:

Intraparticle porosity = $(1- \rho_g / \rho_t)$,

Interparticle porosity = $(1- \rho_b / \rho_g)$, and

Total porosity = $(1- \rho_b / \rho_t)$

Where ρ_b- Bulk Density, ρ_g- Granular Density, ρ_t- True density.

Packability: Sufficient amount of sample was poured slowly and gently into a 25 ml measuring cylinder and tapped for 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100 and 1200 times. The packability was evaluated by the tapped density according to the Kawakita and Kunos methods (equation 1)(12).

$$n/C = 1/ (ab) + N/a \quad \text{...(equation 1)}$$

Where n is the tap number, C denotes the volume reduction which can be calculated according to the Equation 2, 1/a defines the degree of volume reduction at the limit of tapping, termed compactibility and 1/b is a constant related to cohesion, termed cohesiveness.

$$C = (V_o-V_n) / V_o \quad \text{...(equation 2)}$$

Where V_0 and V_n are the powder bed volumes at initial and n^{th} tapped state, respectively

The plot of n/C versus n is linear and the compactibility 1/a and cohesivity 1/b are obtained from the slope (1/a) and the intercept (1/ab) of the plot.

Preparation of tablets: - The different batches of different type of tablets were prepared. Batch detail of different types of tablets is given in table 1.

Table 1: Batch details of tablet prepared by wet granulation, direct compression with conventional OFX and direct compression with agglomerates of OFX

Ingredients (Mg.)	**OFX-WGT***	**OFX-DCT****	**OFX-SCT*****
OFX	250	250	------
OFX-SC	------	------	250
Avicel	112.5	112.5	112.5
Croscarmellose sodium	30	30	30
Polyvinylpyrollodine	2% w/v	------	------
Magnesium stearate	7.5	7.5	7.5
Total weight(mg)	400	400	400

*OFX-WGT: Tablets prepared by wet granulation method,
**OFX-DCT: Tablets prepared by direct compression method with conventional OFX, ***OFX-SCT: Tablets prepared by direct compression method with spherical agglomerated crystals.

OFX-SCT (Tablets from spherical agglomerated crystals): Sift the prepared crystals through sieve no # 22 and weighted in specified amount (as shown in table 1). Mix the agglomerated crystals with weighted quantity of avicel and croscarmellose sodium. To the above unlubricated blend add weighted quantity of magnesium stearate. Use this lubricated blend for compression of tablets using Cadmach punching machine (16 stations).

OFX-WGT (Tablets by wet granulation method): The prepared granules were taken for further compression into tablet using Cadmach punching machine (16 stations).

OFX-DCT (Tablets by direct compression method): Compress the ofloxacin raw crystals with directly compressible excipients (avicel and croscarmellose sodium) by lubricating the blend with magnesium stearate and compression of tablets was done by using Cadmach punching machine (16 stations).

Evaluation of prepared tablets:

Prepared tablets were evaluated for following parameters:

Drug content: Three samples viz. OFX-SCT, OFX-WGT & OFX-DCT of 250mg equivalent of ofloxacin was crushed, accurately weighed & transferred to 100ml standard conical flask. 100ml of buffer of pH 1.2 was added to dissolve the OFX-SCT, OFX-WGT & OFX-DCT. The solution was filtered through Whatman filter paper and diluted the solution. The absorbance was taken at 294nm. Calculate the content of tablets using calibration curve.

Disintegration study: Disintegration test was carried out using Electrolab disintegration test apparatus.

Friability test: Twenty tablets were weighted and placed in the Roche friabilator rotated at 25 rpm. After revolutions the tablets were dedusted and weighted again. The friability was measured using equation 3,

$$\%F = \{1- W / W_0\} \text{ X } 100 \qquad \text{…..(equation 3)}$$

Where, %F = Friability, W_0 = Initial weight of tablets and W = Weight of tablet after revolution.

Thickness: Three tablets selected randomly from each batch and thickness was measured using Vernier Calipers.

Hardness: Hardness was measured using Monsanto hardness tester; hardness values are shown in Newton.

Dissolution study: The *invitro* dissolution studies were carried out using 8 Station USP type-I dissolution apparatus (Electrolab, Mumbai, India). 900ml of buffer of pH 1.2 was used as dissolution medium. The dissolution medium was kept in a thermostatically controlled water bath, maintained at 37 ± 0.5^0C. The basket containing tablets was rotated at 100 rpm. At predetermined time intervals between 0 and 120 min, 5 ml of dissolution medium was withdrawn and analyzed for the drug release. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask. The absorbance was measured by UV-Spectrophotometer (Shimadzu, Tokyo, Japan) and calculated the amount of drug release by using the calibration curve.

Table 2: Powder characteristics of conventional Ofloxacin, wet granules and agglomerated crystals of OFX.

Parameters	OFX[I]	OFX-WG[II]	OFX-SA[III]
Loose bulk density	0.408±0.008	0.3270±0.005	0.408±0.008
Tapped bulk density	0.666±0.013	0.416±0.005	0.5±0.007
True Density	0.850±0.007	0.580±0.004	0.694±0.004
Intraparticle Porosity	0.216±0.021	0.277±0.010	0.279±0.014
Interparticle Porosity	0.399±0.017	0.216±0.008	0.188±0.006
Total Porosity	0.518±0.006	0.430±0.012	0.416±0.013
Angle of Repose	41.34±1.291	30.45±1.952	29.35±0.433
Carr's Index	39.93±1.709	21.64±0.644	18.87±0.822
Hausner's Ratio	1.63±0.3	1.276±0.01	1.232±0.0126
A	0.614±0.013	0.502±0.015	0.481±0.013
B	0.018±0.001	0.022±0.002	0.027±0.001

[I]OFX: Ofloxacin conventional powder,
[II]OFX-WG: Ofloxacin granules prepared by wet granulation technique,
[III]OFX-SA: Ofloxacin crystal prepared by spherical agglomerates.

Table 3: - Evaluation parameters of prepared tablet

Tablet code	Drug Content (%)	Disintegration Time (min)	Friability (%w/w)	Thickness (mm)	Hardness (Kg)
OFX-WGT	98.4±1.31	3:20. ±0.40	0.95±0.08	3.45 ±0.02	20.1±0.05
OFX-DCT	99.2±1.28	1:38. ±0.41	1.2±0.05	3.37±0.005	20.2±0.05
OFX-SCT	97.4±1.37	1:16. ±0.29	0.8±0.05	3.35±0.01	20.3±0.05

Values with ± shows standard deviation of triplicate readings

Results and Discussion:

Agglomerated crystals of OFX were prepared by Quasi-Emulsion solvent diffusion method. Chloroform, ethanol and water were used as a solvent system. Drug solution was prepared using good solvent (chloroform) and bridging agent (ethanol) furthermore emulsion was formed by dispersing the drug solution into poor solvent (water). Agglomerated crystals were formed due to the diffusion of water into emulsion droplets and further drug crystallized in a controlled manner. Amount of bridging agent play an important role during the crystallization mechanism because bridging agent promote the transfer of drug to a third emulsified phase in which crystal agglomerate densify and grow spherically. In this work when 1ml of ethanol was added, no agglomeration was occurred in the system, may be due to insufficient amount of bridging agent for solubilization, responsible for incomplete wetting of agglomerates. When 3 ml of ethanol was added, the rate of agglomeration formation was more with a uniform spherical shape. Again, when 5 ml of ethanol was added, yield was same as previous one but the shape of agglomerate was quite irregular. The response of amount of bridging agent indicate that the agglomeration may result from the coalescence mechanism of agglomerates with the available bridging liquid upto a certain limit. Therefore, the agglomerate grew in size as the response of speed of agitation. Size and shape regularity of agglomerates were studied by the influence of agitation speed. It was observed that with increasing the agitation speed, the average size of agglomerates decreases with high rate of irregularity in shape. This may be due to decreased thickness of bridging layer absorbed on the surface of agglomerates, leading to the reduction in the coalescence in controlled manner. Agitation at 800 rpm was found suitable for the formation of aggregates with large size and increase regularity. Similarly, effect of temperature was determined; by perform the process at room temperature, 50^0C and 70^0C. It was observed that by increasing the temperature of system, large amount of agglomerates were formed, probably this response of temperature is due to increased solubility of drug in system, leads increased rate of agglomerations. The 50^0C temperature was found suitable for the process. At 70^0C solvent system vaporized, leads decrease agglomeration efficiency. A photomicrograph of optimized batch is show in figure 1.

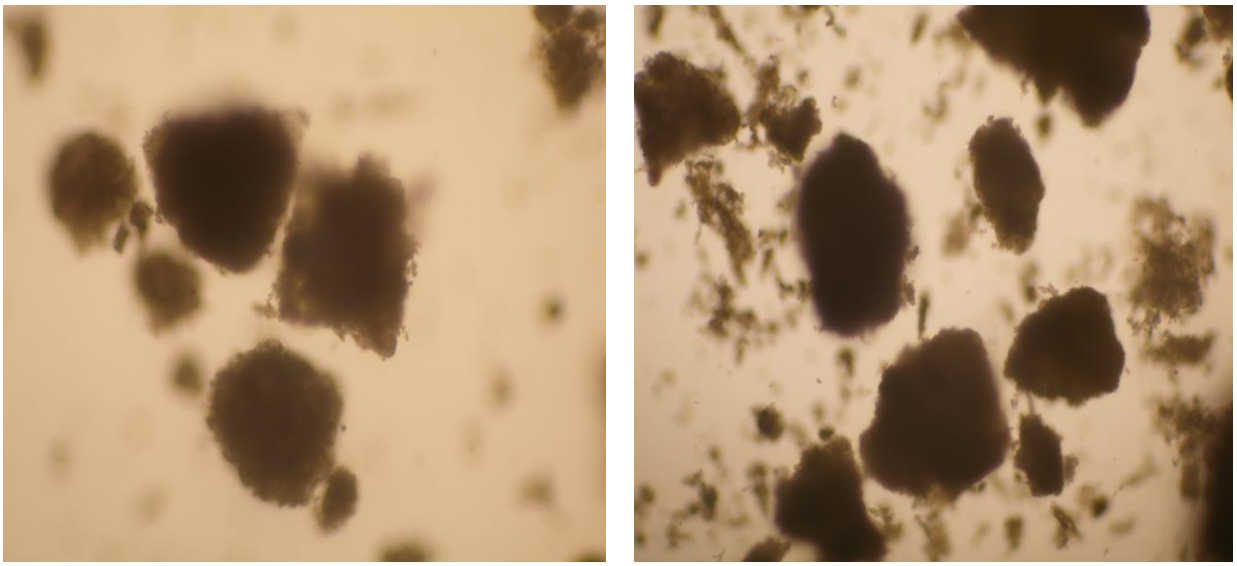
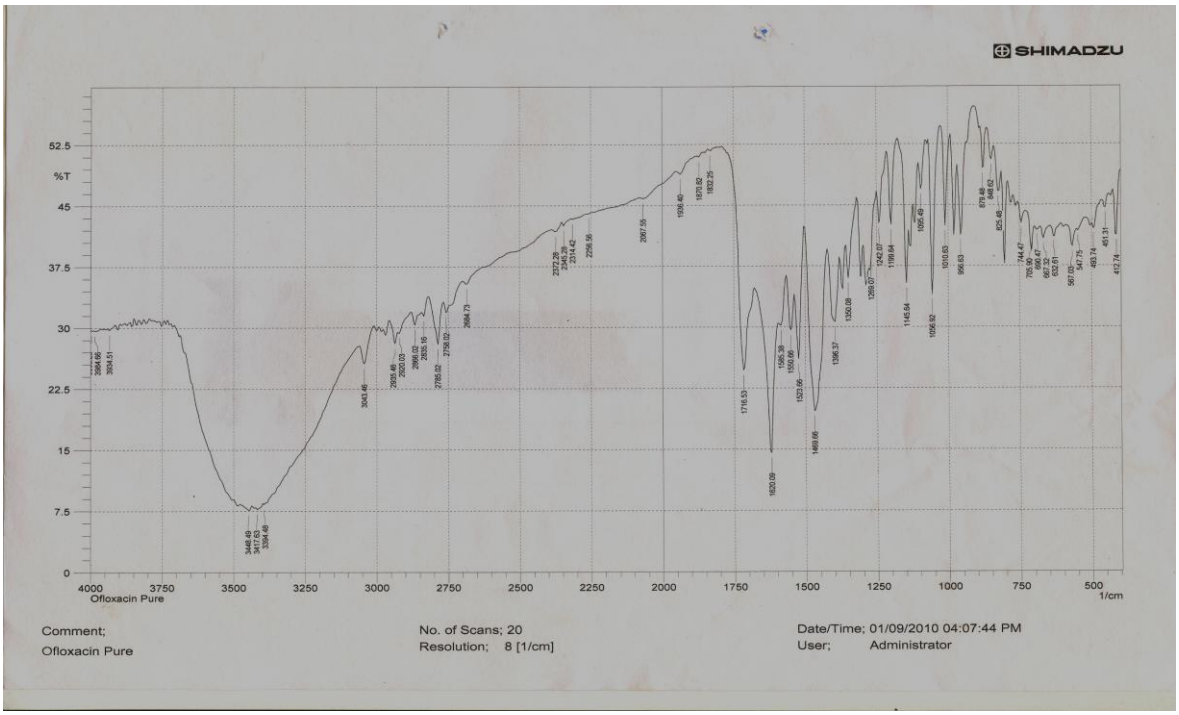


Figure 1: Photomicrograph of optimized spherical agglomerates of OFX

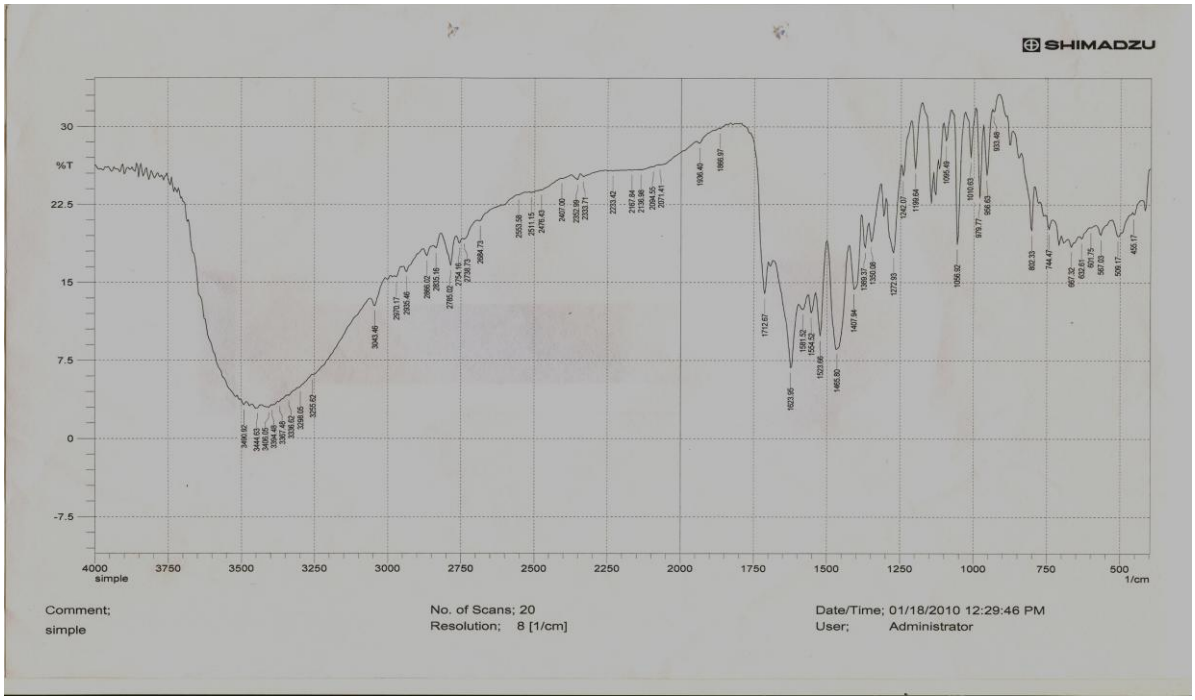
Results of FTIR study are illustrated in figure 2. IR spectra of the agglomerated crystals and granules clearly showed that no significant changes occurred in chemical nature during agglomeration process. Thus the

procedure used for the preparation of agglomerates involves only physical changes of particulate materials, rather than chemical interaction.

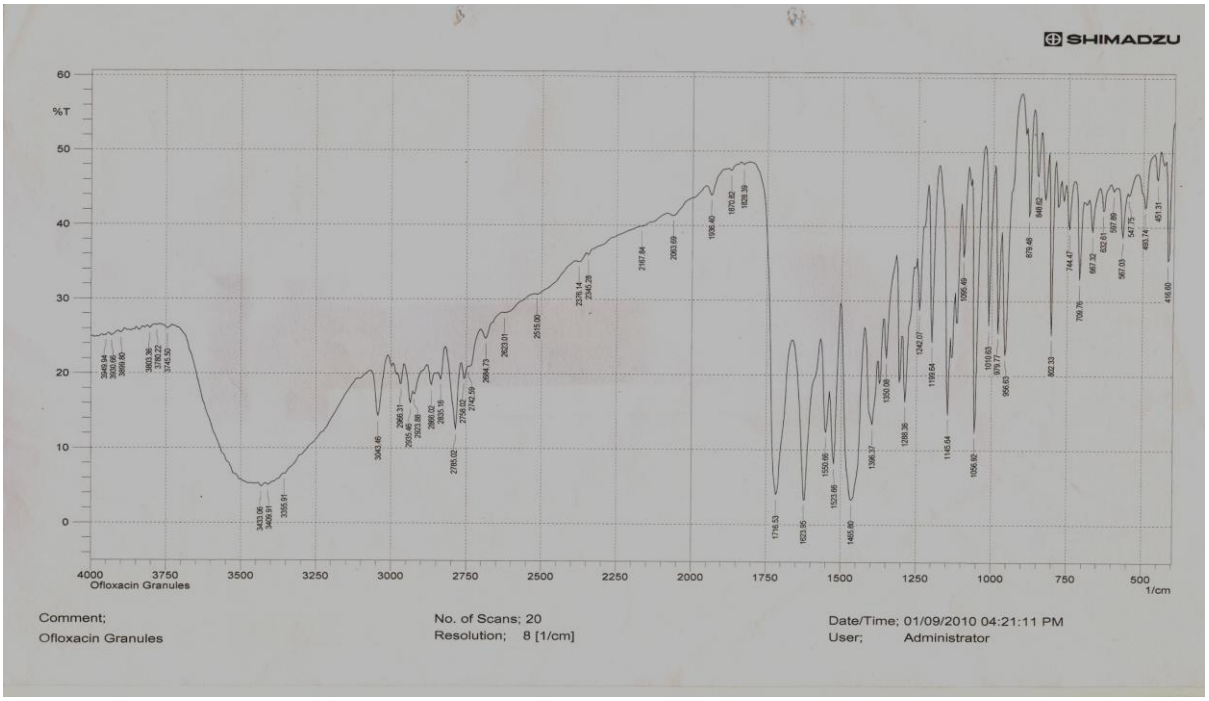
From the data obtained by evaluation of agglomerated crystals, granules of OFX and conventional OFX, the particle size distribution, shape of particles, flowability, and packability were significantly improved for agglomerated crystals. Increased particle size may be the result of aggregation in particles influenced by bridging agent. Spherical shape of prepared agglomerated crystals may be the results of particles agitation of solvent system during process. The improvement in flow property of spherical crystals may be the result of significant reduction in inter-particle friction (due to their spherical shape and a lower static charge). Powder characteristics of conventional OFX, granules and agglomerated crystals are given in table 2. After the evaluation for precompression parameters the compression was carried out for preparation of tablets and further evaluation was performed for every batch of tablets. The compression behavior of prepared agglomerated crystals found to be improved in comparison of granules and conventional OFX which may be due to enhances the plastic inter particle bonding, resulting in a lower compression force required for compressing the agglomerates under plastic deformation compared to that of single crystals. The parameters of drug content, disintegration, friability, thickness, hardness show significant improvement for OFX-SCT. Since the dissolution and bioavailability of drug depends upon particle size, particle density and specific surface area of the agglomerated crystals. In spherical agglomerated crystals the apparent specific surface area increases, tabletting compacts partially breaks the agglomerated crystals thus the average particle size is reduced. But the compression also increases the particle density, which may adversely affect dissolution. The specific surface area of crystals is found to depend on the method used for spherical crystallization. Tablet parameters and comparison of dissolution profile are given in table 3 and figure 3 respectively.



(a)



(b)



(c)

Figure 2: FT-IR spectra of (a) OFX, (b) OFX-SC & (c) OFX-WG.

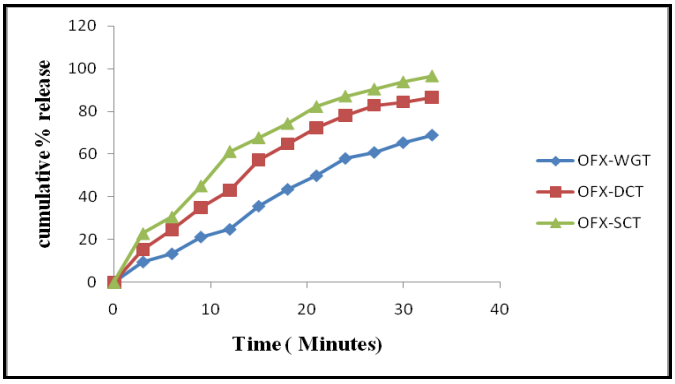


Figure 3: Dissolution profile of tablets prepared from granules, direct compression & spherically agglomerated crystals.

Conclusions:

It can be concluded that spherical agglomerated crystallization process may be an alternative and effective method for preparation of tablet for improvement of the solubility and thus bioavailability of poorly soluble drug. This technique also be helpful and may be successful in industrial point of view due to the general popularity of tablet as a suitable and most acceptable dosage form for delivery of the various kinds of drug.

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