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Enhanced solubility and dissolution rate of telmisartan by quasi emulsion solvent diffusion and spherical agglomeration techniques: A comparative study

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ABSTRACT

Telmisartan (TEL) is a class of angiotensin receptor blocker, used in the treatment of hypertension. The poor solubility and dissolution rate of drug leads to its limited bioavailability (< 50%). The aim of this study was to improve the solubility and dissolution rate of TEL using spherical agglomeration technique. Quasi emulsion solvent diffusion (QESD) and simple spherical agglomeration (SA) techniques have been selected, utilized and compared for their effectiveness in improving the solubility and dissolution rate. Based on drugs solubility N, N dimethyl formamide (DMF), chloroform and water were selected as good solvent, bridging liquid and poor solvent respectively for spherical agglomeration. Optimization of all possible parameters for favourable spherical crystallization was done successfully. Results indicated that, agglomerates obtained by QESD technique showed better improvement in solubility (2.89 and 2.30 folds in 0.1N HCl and 7.5 pH phosphate buffer respectively) and dissolution rate (2.81 fold) compared with pure drug. Results of FTIR showed no interaction between the drug and solvent, XRD patterns showed partial amorphization of drug and SEM photographs confirmed the spherical shape and microscopic crevices on the surface leads to better wettability. Thus, QESD technique is less expensive and simple technique for improving the solubility and dissolution rate of TEL.

KEY WORDS: Telmisartan, Spherical Agglomerates, Solubility, Dissolution Rate.

1. INTRODUCTION

Telmisartan (TEL) an antihypertensive agent, used in the treatment of hypertension and also indicated for reducing the risk of myocardial infarction, stroke, or death from cardiovascular causes. It is a class of angiotensin receptor blocker (ARB's) with selective binding to angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of action of angiotensin II on vascular smooth muscle, leading to a reduction in arterial blood pressure. TEL is highly hydrophobic in nature with logP value 7.7. Because of its poor aqueous solubility and dissolution rate; bioavailability is limited to < 50% (Stangier, 2000). Moreover TEL is known to be poorly flowable and compressible drug.

Various techniques like micronization, complexation, converting into salt form, solid dispersion and addition of surfactants have commonly been used to increase solubility, dissolution rate and there by oral absorption and bioavailability of many hydrophobic drugs, but still there are some practical limitations. One of the successful and novel approaches to enhance the solubility and dissolution rate is spherical agglomeration. Spherical agglomeration is novel technique that can able to directly transfer the fine crystals produced during the crystallization into a spherical shape. This method gained great attention and importance due to the fact that crystal habit (form, surface, size, and particle size distribution) can be modified during the crystallization process. As a consequence of such modifications in the crystal habit, physicochemical properties like solubility, dissolution rate can be improved drastically along with certain micrometric properties like bulk density, flow property, and compactibility (Mahanty, 2010).

Spherical agglomeration is defined as the process of formation of aggregates of crystals held together by liquid bridges. The agglomerates are formed by agitating the crystals in a liquid suspension in presence of bridging liquid. This technique of spherical agglomeration had been used successfully for hydrophilic drug like meloxicam (Farid, 2010), zaltoprofen (Krishna, 2013), carbamazepine (Javadzadeh, 2009) etc. There are four techinques for the preparation of spherical agglomerates i.e. simple spherical agglomeration (SA), quasi emulsion solvent diffusion method (QESD), ammonia diffusion and neutralization techniques (Bharti, 2013). Out of these techniques SA and QESD techniques were widely used, because of their easy, simple and faster processing relative to other methods.

SA and QESD techniques requires, a three solvent system consisting of a good solvent in which drug is having good solubility, a poor solvent in which drug is insoluble or poorly soluble but must be miscible with good solvent. The interaction between poor and good solvent is stronger than interaction between drug and good solvent, so that immediate crystallization takes place. The third solvent bridging liquid, should be immiscible with poor solvent, but used to wet the drug crystals and acts as binding agent to form agglomerates (Patil, 2010). So, successful preparation of spherical agglomerates requires selection of suitable solvent system and its composition, and

optimization of various processing parameters like, temperature difference, stirring rate, mode of addition of bridging liquid and reaction rate.

In present study an attempt was made to optimize the process of spherical agglomeration for TEL and to compare the efficiency of SA and QESD methods in improving the micromeritic and physicochemical properties of TEL.

2. MATERIALS AND METHODS

Materials: Telmisartan was obtained from Dr. Reddy's Laboratory, Hyderabad, India, as a gift sample. N, N Dimethyl Formamide (DMF), Chloroform and all other chemcials were purchased from Qualigens Fine Chemicals Pvt. Ltd, Mumbai, India. All chemicals used were of analytical grade.

Methods:

Solubility Studies for Pure TEL: Excess of drug was added to each 25 mL of different solvents such as DMF, ethanol, methanol, chloroform, dichlromethane taken in stopperred conical flasks and resulting mixture was treated at room temperature for 12 hrs. After shaking to achieve equilibrium, 5 mL aliquots were withdrawn and filtered through Whatman filter paper. The filtrate was diluted and analyzed by UV- Visible spectrophotometer (Evolution 201, Thermo Scientific) at 295 nm. Solubility of drug in different solvents was determined from the calibration graph (Connors, 1965).

Selection of Solvent Quantities: Selection of solvent quantities (good solvent, poor solvent and bridging liquid) for spherical agglomeration was done using SCHEFFE'S (third degree incomplete) model. According to this model, composition of solvents can be determined by identifying and analyzing different points on the ternary diagram (Martino, 1999).

Optimization of Processing Variables for Spherical Agglomeration: The following variables which affect the process of spherical agglomeration were evaluated (Martino, 1999)

Difference in Temperature: The temperature was kept constant (at 80°C) for drug solution whereas non solvent temperature was modified (RT, 10°C, 20°C) and the influence of temperature was studied.

Agitation Speed: The process of spherical crystallization was tested at different stirring rates viz. 500, 750, 1000 and 1250 RPM, because it influence the characteristics of spherical crystals.

Mode of Addition: The mixture of drug solution and bridging liquid was added in drop wise and whole solution at a time to the non-solvent and the influence of way of addition was studied.

Stirring Duration: After the spherical crystallization the influence of residence time or duration of stirring was tested by continuing the agitation for 5 - 10 min, because it influences the size of the crystals formed.

Preparation of Spherical Agglomerates:

Preparation of TEL Spherical Agglomerates using QESD Technique (F1): TEL (1.0 g) was dissolved in 25 mL DMF (good solvent) and heated to 80°C to form saturated solution, and then 5 mL chloroform (bridging liquid) was added at room temperature (35°C) and mixed well. The solution was poured drop wise into 75 mL of distilled water (poor solvent) under stirring rate of 1000 (± 50) rpm using a propeller type of agitator (Remi motors, India) maintained at temperature 10°C using thermostat. After agitating the system for 5 min, the formed agglomerates were collected by filtration through Whatman filter paper (No. 1) under vacuum. Separated spherical crystals were placed at 45°C for drying in a hot air oven for 24 hrs and then stored in desiccators (Farid, 2010).

Preparation of TEL Spherical Agglomerates using SA Technique (F2): TEL (1.0 g) was dissolved in DMF (25 ml) and heated to 80°C to get clear solution. This saturated solution of drug was poured quickly into distilled water (70 ml) under constant stirring using a controlled speed mechanical stirrer (Remi motors, India) at 1000 ± 50 speed, maintained at temperature 10°C using thermostat. When fine crystals of TEL began to form 5 ml of chloroform was added drop wise. Thereby bridging liquid collects the crystals suspended in the system by forming liquid bridges between them and finally spherical agglomerates were formed. After agitating the system for 5 min, formed agglomerates were collected by filtration through Whatman filter paper (No.1) under the vacuum. Separated spherical crystals were placed at 45°C for drying in a hot air oven for 24 hrs and then stored in desiccators (Krishna, 2013).

Evaluation of Spherical Agglomerates:

Infrared Spectroscopy: The pure drug and prepared spherical agglomerates were analysed by FTIR spectrophotometry (Alpha, Bruker) using KBr disk method. About 1 mg of sample was triturated with 100 mg of dry, finely powdered KBr. The mixture was compressed into a disc and analysed in the range from 400 to 4000 nm.

Powder X-ray Diffraction Studies: The powder X-ray diffraction patterns of pure drug and prepared agglomerates was recorded using X-ray Diffractometer (Rigaku Miniflex II), with Ni filtered radiation of wavelength 1.5406 Å (Cu Target). Samples were scanned in the 2θ range of 0 - 50^0. The scanning speed used for the recording was 3^0/min with step size of 0.02^0. Diffraction pattern was analyzed using multi dimension minimization program.

Scanning Electron Microscopy (SEM): The small sample of prepared agglomerates was mounted directly on directly on the SEM sample stub, using double-sided sticking tape, and coated with a gold film (thickness 200 nm) under reduced pressure (0.001 torr) and photographed. Coated samples were analysed in a SEM Model Joel- LV-5600 (Zhou, 2007).

Flow Properties: TEL and prepared spherical agglomerates were evaluated for bulk density (ρ_b) and tapped density (ρ_t) using density apparatus (TDA2, Campbell Electronics). The Carr's index and Hausners's ratio were then calculated by using ρ_b and ρ_t. The angle of repose was determined by fixed funnel method (Baxter, 2003).

Particle Size: Size of the prepared agglomerates was evaluated using calibrated optical microscope. About 100 individual particle sizes were measured; their size range and mean diameter frequency were calculated. Then average particle size was calculated (Indian Pharmacopoeia, 2010).

Solubility Studies: Solubility studies were performed according to method reported by Higuchi and Connors. Excess of pure TEL and prepared agglomerates were added to each 25 mL of distilled water, 0.1 N HCl and pH 7.5 phosphate buffer solution taken in stopperred conical flasks and resulting mixture was treated at 37± 0.5^0C temperature with 100 rpm in an incubator orbital shaker for 24 hrs. After shaking to achieve equilibrium, 2 mL aliquots were withdrawn at 1 hr intervals and filtered through Whatman filter paper. The filtrate was diluted if necessary and analyzed by UV- Visible spectrophotometer at their respective λ_{max} (288, 295 and 291 nm). Solubility was determined from the calibration graphs (Connors, 1965).

Drug Content and Yield: 100 mg of each formulation were taken and ground to powder, then 50 mg of powder was taken in 50 mL volumetric flaks and dissolves in pure methanol and mixed thoroughly by shaking. The volume was made upto 50 mL and filtered through whatman filter paper. Then filtrate was diluted suitably with 7.5 phosphate buffer and absorbance was measured at 295 nm using UV/Visible spectrophotometer. Drug content and percentage of yield were calculated from standard calibration curve (Zhong, 2014).

Dissolution Studies: *In Vitro* dissolution studies were carried out using USP type –II apparatus using 900 mL of pH 7.5 phosphate buffer as medium maintained at 37± 0.5°C temperature and operated at 75 rpm. An accurately weighed quantity of 40 mg each of pure TEL and prepared agglomerates were subjected to test. 5 mL samples were withdrawn at predetermined time intervals (5, 10, 15, 20 up to 60 min) and replaced with equal volume of fresh medium. Collected samples were filtered diluted if necessary and analyzed by UV- Visible spectrophotometer at 295 nm. The dissolution data obtained was evaluated for its order of drug release. Then the dissolution kinetic parameters and dissolution efficiencies were calculated (USP, 2011).

Stability Studies: The selected formulation (F1) was evaluated for its stability at 40 ± 2°C / 75 ± 5 % RH for about 3 months as per ICH guidelines. The samples were taken out after 3 months and evaluated for the drug content; solubility and *in vitro* release study (Guidelines, 2003).

3. RESULTS AND DISCUSSION

Solubility Studies for Pure TEL: From the results of solubility studies of pure TEL, DMF was selected as good solvent because of its solubilizing nature compared with ethanol and methanol. Water was selected as poor solvent because TEL is practically insoluble in water. Chloroform was selected as bridging liquid because of its excellent wettability with the drug and immiscibility with water.

Selection of Solvent Quantities: According to this model, composition was determined by identifying points on the ternary phase diagram (XYZ). Parallels of the three sides of the triangle are drowning through the middles of side, four new triangles were traced, on which seven points were determined in a same way as for the first triangle. Total of 19 points were identified and executed for formation of stable agglomerates in three stages.

Stage-1: Seven experimental points were identified from the triangle XYZ (figure.1B), named them as A, B, C, D, E, F and G. Seven trails were conducted using corresponding percentages of solvents to prepare spherical agglomerates. Results of these trails were given in table.1. Results indicated that, region nearer to B was expected to get spherical agglomerates.

Stage- 2: For a thorough study, triangle HIY (figure.1C) was more closely investigated after division into four triangles in the same way as previously described. The new points identified were a, b, c, d, e, f and B. In fact point B is already done in previous stage. Here, six trails were performed and results of these trails were given in table no. 2. Results indicated that, composition at 'e' was considered good when compared with point 'a'. This was because crystallization of drug taken place quickly and completely.

Stage- 3: At last, close investigation of triangle 'gde' (figure.1C) enabled to find the best proportion for spherical crystal obtention. Likewise above six experimental points were identified and named as i, ii, iii, iv, v and vi. All these six proportion were executed to prepare agglomerates and results were given in table.3. Results confirmed that point 'i' i.e. 25 % DMF, 70 % water and 5 % chloroform was found to produce spherical agglomerates in single phase without any sticking of drug to stirring element. So, the same was taken for the further studies.

These results postulates that, highest quantity of chloroform leads to phase separation due to insufficient DMF. Increased content of chloroform lead to sticking of drug to rotating element and also converted to paste like consistency, due to enhanced agglomeration of drug. Increased content of DMF leads to formation of cloudy suspension due to insufficient poor solvent to crystallize the drug completely. Decrease in the proportion of chloroform leads to presence of agglomerates along with recrystallized drug due to incomplete agglomeration.

Optimization of Processing Variables: Using the selected solvent, various processing variable which effects the spherical agglomeration were evaluated. Observations from the finding were given in table.4. Results confirmed that, the process of spherical agglomeration performed using 10°C temperature of non-solvent at 1000 RPM, with drop wise addition of drug solution was found to produce best quality agglomerates after 5 min of reaction time.

These results postulate that, higher temperatures produce irregular crystals due rapid evaporation of chloroform leads to inefficient of agglomeration. Lower stirring rates form clumps due to insufficient shear force to break, higher speeds leads to small and irregular agglomerates due to formation of small quasi emulsion droplet early in the preparation. A higher time of reaction produces fines due to destroying the formed crystal agglomerates. Drop wise addition of drug solution formed spherical agglomerates with good geometry due to greater contact time of droplet in the system and counter diffusion of DMF and water. Whereas addition of solution at a time formed uneven sized crystals with irregular geometry, this might be due to rapid crystallization of drug when suddenly exposed to poor solvent.

Characterization of Agglomerates:

Infrared Spectroscopy (FTIR): FTIR spectral studies were performed to determine the interaction between the TEL and solvents used in the spherical agglomeration. FTIR spectrum of pure TEL (figure.2a) showed characteristic peaks at wave numbers 3058.50 cm^{-1} (aromatic C–H stretching), 2923.78 cm^{-1} (aliphatic C–H stretching), 1694.94 cm^{-1} (–COOH acid), 1599.40 cm^{-1} (aromatic C=C bending and stretching), 1448.24 cm^{-1} (C–H bending), 1382.13 (OH bending and C=0 stretching of –COOH) and 795.47 cm^{-1}, 740.97 cm^{-1} (ring vibrations due to 1,2 – di-substituted benzene). Similar characteristic peaks with slight variation in their wavelength were observed with agglomerated drug (figure.2b & c). This indicated the compatibility between the drug and solvents used.

Powder X-ray Diffraction Studies: The PXRD patterns of pure and agglomerated drug (figure.3) confirms that, the prepared spherical agglomerates were crystalline in nature but with change in their crystalline nature compared with pure drug. The diffraction pattern of pure drug displays high crystallinity, specified by various distinct peaks at diffraction angles of 2θ (7.0°, 14.0°, 23.0° and 25.0°) during the scanning range. On other hand spherical agglomerates shows a significant change in degree of crystallinity, evident by the slight fading of sharp distinctive peaks. Form this partial amorphization of drug was expected. This might be attributed to change in orientation of crystals during the growth phase. The agglomerates prepared by QESD (F1) showed more fading in distinctive peaks compared with agglomerates prepared by SA (F2). This might be due to diffusion of normal crystal agglomeration associated with SA method rather than diffusion.

Scanning Electron Microscopy (SEM): SEM images of prepared agglomerates are shown in figure.4, confirmed that the agglomerates formed were spherical in shape and the surface of the agglomerates was rough with numerous microscopic pores, crevices and cracks. They were formed by the cluster of Telmisartan crystals.

Flow Properties: Results of angle of repose, bulk density, true density, Hausner's ratio and Carr's index are given in table.5 and were used to determine the flow, compressibility and packagebility of material. Angle of repose, Hausner's ratio and Carr's index values of pure TEL were 43.12^0, 1.15 and 33.92 % respectively, indicating its poor flow and compressibility. Whereas, the prepared spherical agglomerates improved the flow properties (angle of repose: F1- 28.6 & F2- 28.31) and compressibility (Carr's index: F1-10.75 & F2-8.30), indicates the suitability of agglomerated to direct compression without any further processing.

Particle Size: Results of particle size analysis are given in table no. 6 indicated that, agglomerates prepared with SA method were found to have bigger size (403.01 µm) compared with the size of the agglomerates (257.86 µm) prepared with QESD method. This was due the formation of agglomerates by coalescence of microcrystalline precipitate in SA method, whereas in QESD method agglomerates forms by counter diffusion of solvents from quasi droplets. The sizes of agglomerates were further confirmed from the SEM analysis.

Solubility: Results of solubility studies were given in table.6, indicated that, compared with pure drug, solubility of agglomerates prepared with QESD method showed better improvement in the solubility (2.89 and 2.30 folds in 0.1N HCl and pH 7.5 phosphate buffer respectively), than SA method (2.26 fold and 1.44 folds in 0.1N HCl and pH 7.5 phosphate buffer respectively). This might be due to decreased primary particle size, improved porosity and partial amorphization of drug in agglomerates as demonstrated by XRD studies.

Drug Content and Yield: Results of drug content and yield are given in table.6, indicated that, there is no considerable loss of drug during the manufacturing and the prepared agglomerates showed excellent drug content.

Dissolution Studies: Dissolution data of pure drug and prepared agglomerates are given table.7, and the profile is shown in figure.5. The prepared agglomerates exhibited excellent improvement in the dissolution rate compared with pure drug. This could be attributed to the improved porosity and partial amorphization of drug as evident from XRD studies. Agglomerates prepared by QESD method showed better improvement in dissolution rate compared with SA method, due to its small particle size, more surface area and fastest rate of wettability. Drug release form the prepared formulations followed first order release kinetics with DE_{60} - 13.17, 38.72 & 34.30 % and T_{50} – 146, 45 and 52.56 min respectively for Pure TEL, F1 and F2.

Stability Studies: After 3 months of storage, there was no considerable difference in the drug content, solubility and *in vitro* release pattern of spherically agglomerated TEL, when compared with zero time. Indicate that prepared agglomerates were quite stable.

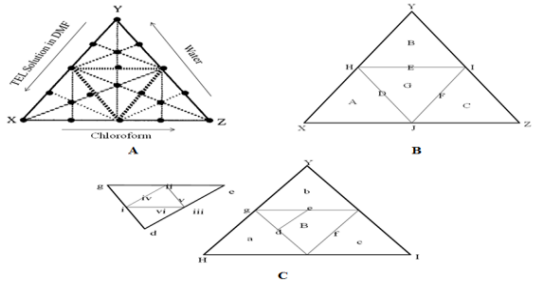

Figure.1. Scheffe's Ternary Diagram of TEL Sol in DMF, Chloroform and Water

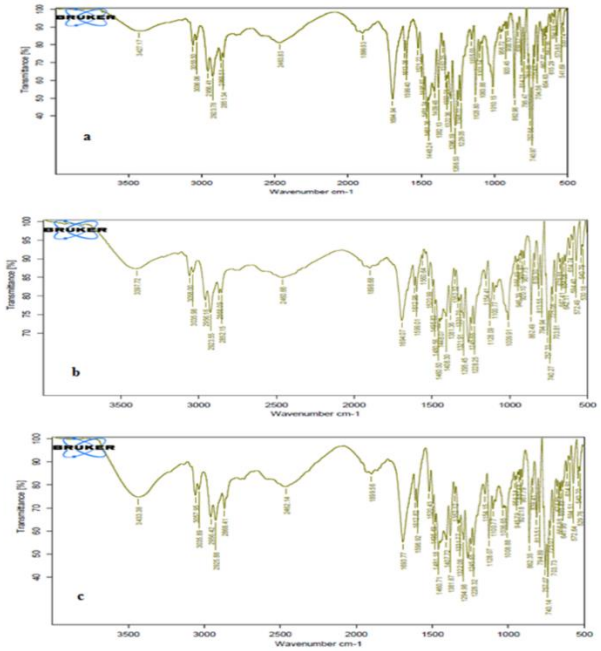

Figure.2. FTIR Spectra of Pure TEL (a) and Agglomerated TEL Prepared by QESD (b) & SA (c) Techniques

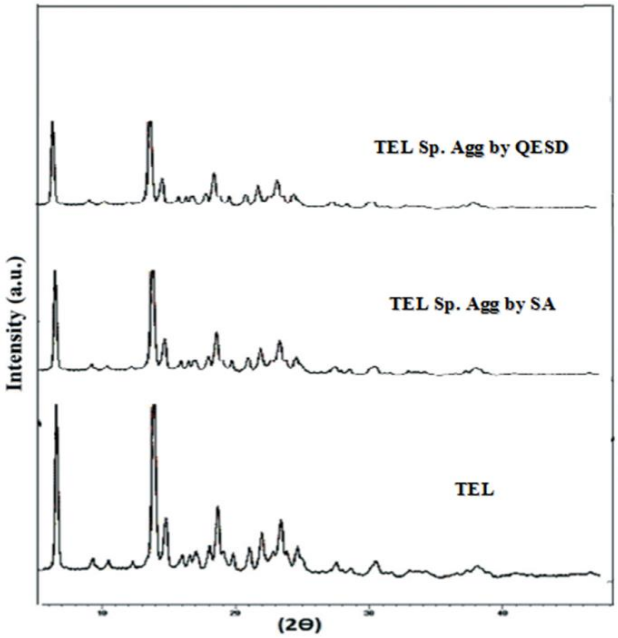

Figure.3. PXRD Patterns of TEL Pure Drug Compared with Agglomerates Prepared by QESD & SA Techniques

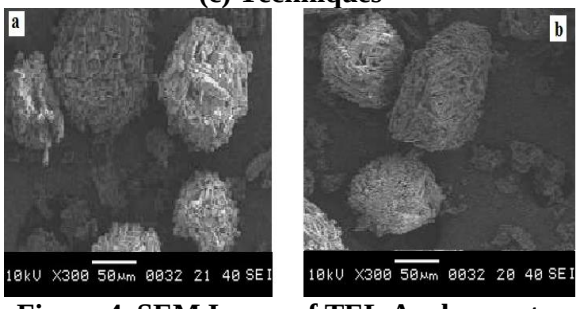

Figure.4. SEM Image of TEL Agglomerates Prepared by QESD (a) & SA (b) Techniques

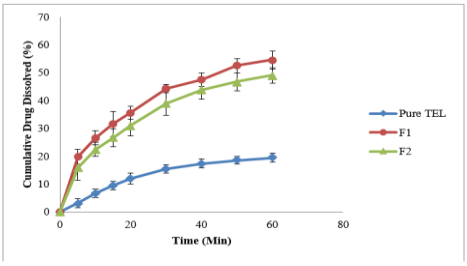

Figure.5. Dissolution Profile of Pure TEL and Prepared Spherical Agglomerates

Table.1. Results of the Experiments Corresponding to the Seven Points of Scheffe's Ternary Diagram in Figure 1B

Zone Code	% of DMF	% of water	% of Chloroform	Comments
A	70	20	10	Turbid/ Cloudy Suspension
B	20	70	10	Round Agglomerates, Drug Stick to the Stirring Element
C	10	20	70	Two Separate Phases
D	50	25	25	Two Separate Phases with Turbid/ Cloudy Suspension in Aqueous Phase
E	25	50	25	Two Separate Phases with Turbid/ Cloudy Suspension in Aqueous Phase
F	25	25	50	Two Separate Phases with Turbid/ Cloudy Suspension in Aqueous Phase
G	33	33	33	Two Separate Phases with Turbid/ Cloudy Suspension in Aqueous Phase

Table.2. Results of the Experiments corresponding to the Seven Points of Scheffe's Ternary Diagram in Figure 1C

Zone Code	% of DMF	% of water	% of Chloroform	Comments
a	34	58	8	Round Agglomerates in single phase + Re-crystallized Drug in Suspension
b	8	84	8	Two phases, Round Agglomerates at Interface
c	8	58	34	Two phases, Round Agglomerates at Interface
d	25	62.5	12.5	Paste Like Appearance
e	12.5	75	12.5	Round Agglomerates in single phase + Re-crystallized Drug in Suspension
f	12.5	62.5	25	Paste Like Appearance
B	20	70	10	Round Agglomerates, Drug Stick to the Stirring Element

Table.3. Results of the Experiments Corresponding to the Six Points of Scheffe's Ternary Diagram in Figure 1C

Zone Code	% of DMF	% of water	% of Chloroform	Comments
i	**25**	**70**	**5**	**Spherical Agglomerates in Single Phase**
ii	20	75	5	Round Agglomerates in single phase
iii	20	68	12	Paste Like Appearance
iv	22.5	72.5	5	Round Agglomerates in single phase
v	20	72.5	7.5	Round Agglomerates, Drug Stick to the Stirring Element
vi	22.5	70	7.5	Round Agglomerates, Drug Stick to the Stirring Element

Table.4. Effect of Variables on Formulation of Spherical Agglomerates

Parameters	Variables	Observation
Temperature (°C)	RT	Irregular Shape Crystals
	20	Irregular Shape Crystals
	10	Ideal Spherical Agglomerates
Agitation Speed (RPM)	500 ± 50	Clumps
	750 ± 50	Spherical & Large
	1000 ± 50	Spherical & optimum
	1250 ± 50	Irregular Shape & Small
Time of Stirring (Min)	5	Spherical Agglomerates
	10	Size Reduction/ Fines Produced
Mode of Addition	At a time	Uneven Sized Crystals of Irregular Geometry
	Drop wise	Spherical Agglomerates

Table.5. Results of Flow Properties

Parameters	Pure TEL	F1	F2
Angle of Repose (^{O})	43.12 ± 0.54	28.67 ± 0.55	28.31 ± 1.15
Bulk Density (gm/cc)	0.444 ± 0.045	0.754 ± 0.018	0.690 ± 0.016
Tapped Density (gm/cc)	0.672 ± 0.021	0.845 ± 0.017	0.753 ± 0.017
Hausner's Ratio	1.51 ± 0.021	1.12 ± 0.033	1.09 ± 0.044
Carr's Index (%)	33.92 ± 0.668	10.75 ± 2.701	08.30 ± 1.728

* Mean ± SD of Three Determinations (n = 3)

Table.6. Results of Physical Evaluation Studies

Parameter		Pure TEL	F1	F2
Yield (%)		---	92.27 ± 2.170	92.84 ± 2.871
Average Particle Size (µm)		---	257.86 ± 16.912	403.01 ± 19.943
Solubility (µg/ml)	0.1 N HCl	920.27 ± 22.667	2663.19 ± 106.13	2084.08 ± 67.47
	pH 7.5 PBS	4.58 ± 0.387	10.54 ± 1.302	6.6 ± 0.619
Drug Content		---	99.34 ± 0.471	99.47 ± 0.412

* Mean ± SD of Three Determinations (n = 3)

Table.7. Dissolution Data of Pure TEL and Prepared Spherical Agglomerates

Time (min)	Cumulative Drug Dissolved* (%)		
	Pure TEL	F1	F2
5	3.14 ± 1.652	19.82 ± 2.741	15.94 ± 4.562
10	6.68 ± 1.487	26.57 ± 2.535	22.44 ± 4.600
15	9.54 ± 1.482	31.58 ± 4.491	26.61 ± 4.945
20	11.97 ± 1.895	35.65 ± 2.390	31.03 ± 3.556
30	15.48 ± 1.426	44.27 ± 1.432	39.01 ± 3.616
40	17.40 ± 1.512	47.51 ± 2.485	43.80 ± 3.555
50	18.55 ± 1.468	52.52 ± 2.537	46.73 ± 2.551
60	19.48 ± 1.656	54.60 ± 3.191	49.04 ± 2.597

* Mean ± SD of Three Determinations (n = 3)

4. CONCLUSION

Spherically agglomerated crystals of TEL were successfully developed for enhancing the solubility and dissolution rate of the drug. The process of agglomeration by QESD method was found to give superior results in improving the solubility and dissolution rate compared with SA method. Whereas both the techniques improved the flowability and compressibility, indicating suitability of agglomerates for direct compression without any further processing.

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