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Original article

Parameters Optimization & Characterization of Formulated Spherical Agglomerates of Telmisartan by Crystallo-co agglomeration Technique

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ABSTRACT:
The main objective of the study was to improve aqueous solubility of poorly water soluble drug. Telmisartan is a BCS class II drug and has low solubility. To enhance the solubility of Spherical Agglomerates of Telmisartan were formulated using Crystallo co- agglomeration Method. Different process parameter like good solvent, bad solvent, agitation time, speed and bad solvent volume were successfully optimized on the basis of various evolution parameters. Various Polymers like HPBC, PEG, PVP were used to enhance poor compressibility, low compressibility and low Compactibility. HPBC imparts sufficient mechanical strength and spherocity, PEG, gives better compressibility to the agglomerates &The PVP increases the strength of agglomerates.
Keywords: Spherical Agglomerates, Crystallo co- agglomeration, Telmisartan, optimization.

1. INTRODUCTION

Saturation Shake-Flask Method (shake-flask method) is based on the phase solubility analysis that was developed 45 years ago and is still considered by most to be the most reliable and widely used method for solubility measurement even today. The sample solution was prepared by addition of an excess amount of drug to the solubility medium, which was a stoppered flask. The amount of solvent in the flask does not need to be measured accurately. Although it is important to ensure that the amount of added material is sufficient to produce a suspension, it is also important to avoid adding an amount of material that will significantly alter the properties of the solubility medium, including its pH. The pH of the suspension was verified after the addition of the compound and at the end of the experiment. It is generally agreed that saturation or equilibrium has been reached when multiple samples, assayed after different equilibration time periods, yield the same result for apparent solubility. The time to reach equilibrium can vary as per the type of agitation used, the active ingredient properties, the amount of material used, and the equilibration method used. With an agitation rate that is adequate to prevent particle agglomeration and to ensure particle contact with the diluent, samples generally reach equilibrium quickly (often within 24 h). However, for poorly soluble compounds, the equilibrium time may be prolonged, well beyond this time period, because of a poor dissolution rate that is further depressed as the equilibrium process advances and the concentration in solution gets closer to the limit of drug solubility. One way to expedite the process is to increase the effective surface area for dissolution. This can be achieved by either sonication the samples prior to equilibrium evaluation. Filtration and centrifugation are both commonly used to separate the saturated solution from the solute phase. The sample solution can be sonicated for few minutes at the start of the saturation period and later at the end was centrifuged to separate the undissolved content. The absorbance of the solution was recorded using UV spectrophotometer to determine the saturated solubility of the drug in particular solvent system [1, 2].

2. MATERIAL AND METHODS

The selection of the solvent system for the agglomeration process depends on solubility and stability of the drug in the solvent system. Water has been reported as a processing (bad

solvent/external phase) medium, and organic solvents (relatively nontoxic) as good solvents (internal phase) and/or bridging liquids in the system design. This sort of solvent selection has been suggested due to scarce requirement of organic solvent (as a good solvent as well as bridging liquid) than that of bad solvent (aqueous external phase) requirement. The bridging liquid should carry out preferential wetting of crystals and form liquid bridges during the process of agglomeration. Simultaneously, the bridging liquid should be immiscible with a bad solvent. If the bridging liquid acts as a good solvent, it means that it performs the dual role of acting as a good solvent and a bridging liquid. Then the good solvent used should be immiscible with the bad solvent to avoid drug loss due to co solvency [3].

The amount of bridging liquid required can be decided by trial and error. It has been observed that the addition of an inadequate amount of bridging liquid shows under wetting of crystals resulting in the generation of smaller sized agglomerates with more number of fines and excess addition of bridging liquid generates bigger sized agglomerates requiring more processing time for completion of the agglomeration process. For selection of a good solvent, the rotary shake flask method was used. The solubility study was carried out using a number of solvents [i.e., water, ethanol, dichloromethane (DCM), acetone, methanol, chloroform, Dimethyl form amide]. Solubility of the drug was determined in various solvent systems and the result is depicted in Table no. 1. It is seen that the drug has the highest solubility in DMF and lowest in water (Figure 1). So, it was concluded that DMF would be considered as a good solvent and water would be a poor solvent for Solvent change method and Chloroform as good solvent and bridging liquid both for Crystallo- co- agglomeration technique. For Neutralization method sodium hydroxide is selected as good solvent and HCl is selected as bad solvent [4, 5].

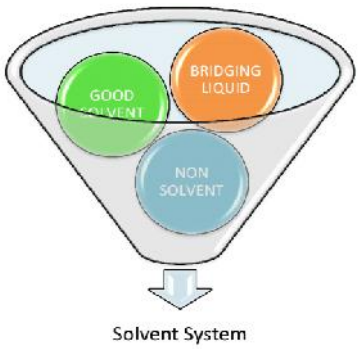

Fig 1: Selection of solvent system

Ternary phase diagram of Telmisartan in three solvent systems: The selection of solvent is dictated by solubility characteristic of drug. A mutually immiscible three solvent system consisting of a poor solvent (suspending liquid), good solvent and bridging liquid are necessary. Physical form of product i.e. whether micro-agglomerate or irregular macro-agglomerates or a paste of drug substance can be controlled by selection of proper solvent proportions. The proportion of solvent to be used is determined by carrying out solubility studies and constructing triangular phase diagram to define the region of mutual immiscibility and miscibility of the three solvent systems.

Procedure:

1. Taken 1 ml of bridging liquid (Chloroform/Dichloromethane) in test tube each time and to it add increasing quantity of distilled water started from 1mL up to 10mL.
2. Taken good solvent in burette and add drop wise to above mixture of water and bridging liquid every time till homogeneous single phase system is obtained.
3. Calculated the respective percentage of water, bridging liquid and good solvent and construct ternary phase diagram for same.

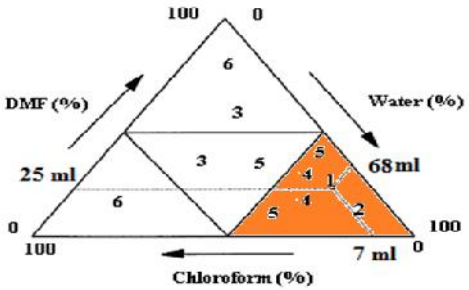

Fig 2: Ternary phase plot

2.1 Selection of solvent quantity for spherical crystallization:

According to this model, composition of solvent can be determined by identifying points on the ternary diagram. If the parallels of the three sides of the triangle are drown through the middles of side, four new triangles are traced, on which seven points are determined in a same way as for the first triangle. As some points are common to both triangles, 19 points can be identified. The points on the vertex correspond to a pure liquid; those on side correspond to a mixture of only two liquids (Table 2; Figure 2). Since the presence of three liquids is compulsory, these points must be excluded. Seven points remain for the experiment; A, B, C, D, E, F and G. Through this study the point on the triangle and the points that enables to find the best proportion for spherical crystallization may be investigated (Figure 3).

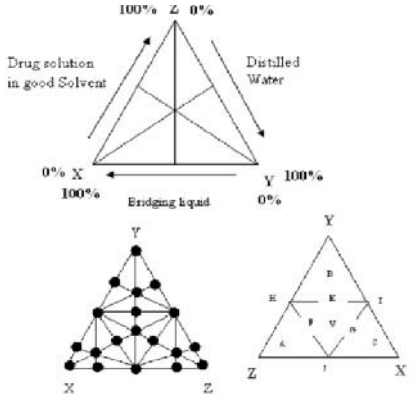

Fig 3: Sheffe´ ternary phase diagrams for selection of proportion of solvents for spherical crystallization.

2.2. Procedure

Telmisartan was dissolved in a mixture of good solvent and bridging liquid in proportions mentioned in table 2 at room temperature to form saturated solution.

According to these model following seven experiments were carried out to check the suitability of the quantity of the solvent system for optimization of spherical crystallization technique. The good solvent with Telmisartan, bridging liquid and poor solvent or dispersion medium yield phase diagram with distant zone or regions.

3. RESULTS AND DISCUSSION

3.1. Optimization and formulation of spherical agglomeration with different hydrophilic polymers

Plain drug agglomerates (without excipients) have shown poor resistance to breaking, poor compressibility, and low compactibility due to inherent poor cohesiveness of the drug. Therefore, it has been suggested to improve these properties by the addition of various polymers like HPBC, PEG, PVP, and so on. It has been reported that agglomerates obtained by the optimum addition of HPBC imparts sufficient mechanical strength and sphericity to the agglomerates, whereas its excess addition leads to the deformation of agglomerates. PEG causes a reduction in the interfacial tension between water and the bridging liquid resulting in a reduction in the force of cohesion between particles. This leads to the generation of spherical agglomerates with a smaller size. PEG, due to its soft and plastic nature, undergoes plastic deformation and gives better compressibility to the agglomerates during the process of compression. The PVP being hard and tough in nature increases the strength of agglomerates (Table 3; Table 4). However, due to its solubility in the bridging liquid (organic solvent), it imparts higher viscosity to the internal phase resulting in increased interfacial tension. The increased viscosity retards the diffusion of the bridging liquid, hampers nucleation and crystal formation, and increases the time for completion of the agglomeration process [6].

3.2. Optimization and formulation of spherical crystallization techniques by changing the process variables:

To optimize the spherical crystallization, several parameters were considered; among these are effect of amount of bridging liquid, effect of the rotation speed, effect of the temperature and effect of mode of addition of bridging liquid [7].

The amount of the bridging liquid is changed to record its effect on crystal formation and the amount of bridging liquid with which spherical agglomerates were prepared was selected. The rotational speed of the stirrer also plays a crucial role in spherical agglomerate formation. If the speed is low large lumps were formed if it is high the formed agglomerates readily gets broken down. The optimal speed of the stirrer is selected for the agglomerates formation (Figure 4). The temperature has a big role to play in agglomeration formation. If the temperature is too less this affects solubility of the drug in good solvent, and if it is too high then the drugs solubility in poor solvent is affected.

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Table 1: Solubility of Telmisartan in different solvents

Solubility in Different organic solvents (mg/ml)						
Water	**Methanol**	**Ethanol**	**Chloroform**	**DMF**	**Dichloromethane**	**Acetone**
0.067 mg/mL	10.132± 0.102mg/mL	3.83± 0.162mg/ml	21.4± 0.113mg/mL	24.6± 0.243 mg/mL	11.123± 0.203g/mL	8.435± 0.302mg/mL

Table 2: Solvent system selections for spherical crystallization of Telmisartan

Technique	Good Solvent	Poor Solvent	Bridging Liquid
Solvent Change	DMF	Water	Chloroform
Neutralization	0.07 M NaOH	0.05 M HCl	Chloroform

Crystallo- co Agglomeration	Chloroform	Water with suitable Diluent	Chloroform

Table 3: Dimethyl form amide-Water-Chloroform Ternary System

S.No	Vol. of water	Vol. of Chloroform	Vol. of DMF				% of water	% of Chloroform	% of DMF
				W1	W2	W3			
1	1	1	3.7	1	1.476	3.5076	16.71	24.66	58.62
2	2	1	3.9	2	1.476	3.6972	27.88	20.58	51.54
3	3	1	4.9	3	1.476	4.6452	32.89	16.18	50.93
4	4	1	5.7	4	1.476	5.4036	36.77	13.57	49.66
5	5	1	6.4	5	1.476	6.0672	39.86	18.76	48.37
6	6	1	7.0	6	1.476	6.636	42.52	10.46	47.02
7	7	1	7.5	7	1.476	7.11	44.91	9.47	45.61
8	8	1	8.0	8	1.476	7.584	46.89	8.65	44.45
9	9	1	8.6	9	1.476	8.3424	47.82	7.84	44.33
10	10	1	9.5	10	1.476	9.006	48.82	7.21	43.97

W1: Weight of water; W2: Weight of chloroform; W3: Weight of DMF

Table: 4 Position of agglomeration formation at specific solvent ratio on Sheffe´ ternary phase diagram

Zone	Good solvent	Poor solvent	Bridging liquid	Comments
A	20	10	70	Thick milky suspension
B	70	10	20	Thick milky suspension
C	20	70	10	Round agglomeration in one phase medium
V	33	33	33	Thick milky suspension
F	50	25	25	Thick milky suspension
G	25	25	50	Thick milky suspension
H	25	50	25	Two separate clear phases

Table: 5 Effect of variables on formulation of spherical agglomerates of Telmisartan

Parameter	Variables	Observation
Percentage (%) of bridging liquid Chloroform	6% **7%** 8%	No Spherical crystals **Spherical crystals** No Spherical crystals
Bridging liquid	**Chloroform** Dichloromethane Toluene	**Spherical crystals** No Spherical crystals Spherical crystals
Agitation speed (rpm)	400±25 **600±25** 800±25	Clumps **Spherical crystals** Irregular shape & small
Agitation time	< 30 min **30 min** > 30 min	Incomplete crystals **Spherical crystals** Breaking of crystals
Temperature	5±2^{0}C 20±2^{0}C 45±2^{0}C	No crystals **Spherical crystals** Large Spherical crystals
Mode of addition of bridging liquid	Whole at a time **Drop wise**	Crystals of irregular geometry **Spherical crystals**

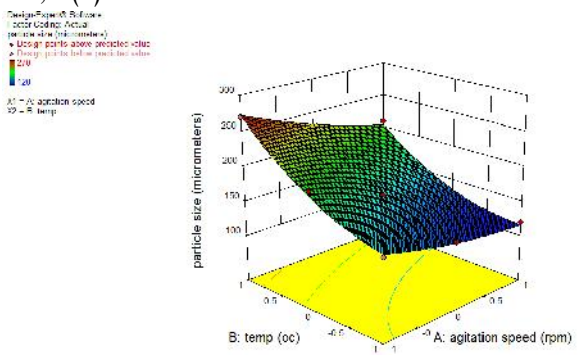

Fig 4: Three dimensional diagram showing impact of temperature and agitation speed of the particle size of Telmisartan agglomerates

4. CONCLUSION

In the CCA technique the drug along with a Diluent talcum was agglomerated by using chloroform as bridging liquid as well as good solvent and water as poor solvent. The recrystallized agglomerates shows improvement in solubility, dissolution rate, Ex- vivo absorption comparative to raw crystals of Telmisartan. The micromeritic properties of agglomerated crystals, such as flow ability, packability, wettability and compatibility were dramatically improved. The main factor in the improvement of flowability and packability was a significant reduction in interparticle friction, due to their spherical shapes and smooth surfaces. Compressibility of the agglomerates was much improved, due to the increased interparticle bonding of agglomerates fractured during compression.

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