RESEARCH ARTICLE

# Potential Screening of Spray Dried Solid Dispersion of Orlistat using Three Dimensional Solubility Parameter

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## Abstract

**Aim:** Hansen solubility parameters (HSPs) have been used to predict the miscibility of a drug with excipients/carriers in solid dispersions. This study investigated whether the miscibility of a drug and its coformer components, as predicted by theoretical miscibility tools, this eventually led to the concept of a three dimensional solubility parameter (E). This is to determine whether the process parameters of the laboratory-scale spray dryer affects the solubility behavior and physical stability of the solid dispersion. Group-contribution method for the estimation of HSPs of pure organic compounds is presented by characteristic groups ensures the prediction of HSP for a broad series of organic compounds including those having complex multi-ring, heterocyclic, and aromatic structures. The predictions are exclusively based on the molecular structure of compounds, and no experimental data are needed. **Materials and Methods:** Theoretical prediction of solubility Fedor's Method/Fedor's Substituent Constants, Hoy's method/Hoy's Molar Attractions, Van Krevelen's solubility parameters the calculation of solubility parameter, and molar volume Van Krevelen's method, which is based on experimental molar volume measured $cm^3Mol^{-1}$, theoretical screening and comparison of orlistat by 3D parameter, formulation of spray dried cocrystals, optimization of spray drying process parameters. **Result and Discussion:** The selected coformer was based on HSP by which three methods are used such as Fedor's methods, van Krevelen's methods, and hoys methods. Based on their given value the selection of coformer was done by Krevelen's $\Delta\delta \leq 5$MP and Greenhalgh $\Delta\delta \leq 7$MP. Proposed structure of orlistat was developed using ChemSketch software. The thorough understanding of the structure of API and coformer is required to locate correctly the hydrogen bonding. Coformer selection was done based on hydrogen bonding in structure. The surface morphology studies revealed that the solid dispersion was closely compacted into small spherical form. **Conclusion:** Considerable improvement in the dissolution rate of orlistat from optimized formulation was due to an increased solubility that is attributed to the supersaturation from the fine cocrystals is faster due to the large specific surface area of small particles and prevention of phase transformation to pure orlistat.

**Key words:** Group contribution methods (Fedor's substituent constants, Hoy's molar attraction constants, and Van Krevelen constants), Hansen solubility parameters, solid dispersion, spray drying process

## INTRODUCTION

A number of methodologies can be adapted to improve solubilization of poor water-soluble drug and further to improve its bioavailability. The techniques generally employed for solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, cosolvency, spray drying solubilization, and hydrotropy. Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. As solubility and permeability are the deciding factor for the *in vivo* absorption of the drug, these can be altered or modified by enhancement techniques.[1] The number of poorly water-soluble compounds has dramatically increased with the advent of combinatorial chemistry and high

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throughput screening. Current drug selection procedures favor drugs of Biopharmaceutical Classification System Class II (low solubility-high permeability); therefore, it is the solubility behavior of such drugs that is the key determinant of their oral bioavailability. Formulation techniques to address this current trend such as particle size reduction, and improved wetting. Several special types of formulation such as amorphous materials and self-emulsifying drug delivery systems can improve the saturation solubility of the drug and enhance oral absorption *in vivo*. Amorphous drugs are advantageous over crystalline drugs, with higher solubility and enhanced bioavailability.[2,3] However, due to their high energy state, they are physically unstable, and stability against crystallization is critical for pharmaceutical development. Because an amorphous drug in a solid dispersion is more stable than the drug in pure amorphous form, due to the interaction between the drug and the polymer carrier, solid dispersion technologies have been widely used in the pharmaceutical industry as a successful strategy to utilize amorphous drugs. It is important in pharmaceutical development for the process parameters of these techniques to be carefully controlled because recrystallization of amorphous drugs negates the advantages of amorphous forms. The preparation of solid dispersions using spray drying has been studied previously, but those studies focused mainly on factors such as the drug-polymer ratio and the compatibility between the drug and the carrier in the solid dispersions.[3]

## Group – contribution methods

These methods have been used to estimate the solubility parameter. Van Krevelen's, Fedor's, and Hoy's method have reviewed these techniques and given tables of group values. The molar volume of solvents and polymers can also be estimated by group contribution techniques. The group contribution values of van Krevelen's and Hoftyzer are based on cohesive energy data of polymers/coformer. The group contribution techniques are based on the assumption that the contributions of different functional groups to the thermodynamic property are additive.[4,29] The group contribution method is used for theoretical calculation which helps for the selection of coformer which is compatible with drug. The Hansen solubility parameter predicts whether drug and coformer is compatible and forms the molecular complex with drug and coformer. The group contribution reduces practical work by predicting whether the molecular complex is formed or not. The Fedor's method, Hoy's method, and Van Krevelen's method calculation is based on the attachment of atom or molecules from the structure. These methods are used for theoretical calculation of solubility. The theoretical prediction or possibility formulation by Krevelen's $\Delta \leq 5$ MP and Greenhalgh $\Delta \leq 7$ MP.[29]

## Methods for estimating solubility parameter/group contribution method

The partial solubility parameters describe the ability of molecule to interact with another one of the some or a different type through intermolecular forces. The molecular force and molar volume are composed by the sum of the contribution of all structural fragments which are present in the molecules.[5,6] Fedor's supposed group contribution to the molar volume of molecules and van Krevelen/Hoftyzer group contribution to the molecular forces by combining both methods, partial solubility parameters can be calculated as follows:[4]

$$\delta_d = \frac{\sqrt{\sum_i Fpi}}{\sum_i Vi} \quad (1)$$

$$\delta_P = \frac{\sqrt{\sum_i F2pi}}{\sum_i Vi} \quad (2)$$

$$\delta_h = \frac{\sqrt{\sum_i Fhi}}{\sqrt{\sum_i Vi}} \quad (3)$$

Where
i = Structural group within the molecules
Fd =Group contributions to dispersion forces
Fp = Group contributions to polar forces
Fh = Group contribution to hydrogen bond energy
Vi = Group contribution to molar volume.

## Solubility parameter

Solubility parameters are termed as cohesion energy parameters and derive from the energy needed to convert a liquid phase to a gas phase. The energy of vaporization is direct measures of the total (cohesive) energy present the liquid's molecules together. All types of bonds present in the liquid together are broken by evaporation, and this has led to the concepts described in more detail later. The term cohesion energy parameter is more appropriately used when referred to surface phenomena.[7,8]

$$c = \frac{\Delta H - RT}{Vm} \quad (4)$$

Where,
C = Cohesive energy density,
H = Heat of vaporization,
R = Gas constant,
T = Temperature,
Vm = Molar volume.

The cohesive energy density of a liquid phase is a numerical value indicating the energy of vaporization in calories per cubic centimeter and is a directly reflecting degree of Van der Waals forces holding the molecules of the liquid together. Such correlation between vaporization and Van der Waals forces also transform into a correlation between vaporization and solubility behavior. This is because the same intermolecular

attractive forces have to be overcome to vaporize a liquid as to dissolve it. The solubility of two materials is only possible when intermolecular attractive forces are quite similar; one might also expect that materials with similar cohesive energy density values would be miscible.[9,10]

### Hildebrand parameters and polymer solution thermodynamics

The Hildebrand solubility parameter is defined as the square root of the cohesive energy density

$$\delta = \sqrt{c} = \left[\frac{\Delta H - RT}{Vm}\right] 1/2 \quad \text{or} \quad \delta = (E/V)1/2 \tag{5}$$

V is the molar volume of the pure solvent, and E is its (measurable) energy of vaporization. The numerical value of the solubility parameter in $MPa^{½}$ is 2.0455 times larger than that in $(cal/cm^3)^{½}$. The solubility parameter is an important quantity for predicting solubility relations.[11,12]

### Hansen solubility parameters (HSP)

A widely used solubility parameter approach to predicting solubility drug and coformer composition in the form of cocrystal on the basis of these so-called HSP is that the overall total energy of vaporization of a liquid consisting of several individual parts such forces are dispersion forces (atomic), (molecular) permanent dipole-permanent dipole forces (molecular), and (molecular) hydrogen bonding (molecular i.e. electron exchange).[13,14] For the saturated aliphatic hydrocarbons, for example, these are essentially the only cohesive interactions, and the energy of vaporization is assumed to be the same as the dispersion cohesive energy, ED. The basic equation which governs the assignment of Hansen parameters is that the total cohesion energy, E, must be the sum of the individual energies which make it up.[15]

$$E = ED+EP+EH \tag{6}$$

Dividing this by the molar volume gives the square of the total (or Hildebrand) solubility parameter as the sum of the squares of the Hansen D, P, and H components.

$$E/V = ED/V+EP/V+EH/V \tag{7}$$

$$\delta 2 = \delta 2D+\delta 2P+\delta 2H \tag{8}$$

To sum up this section, it is emphasized that, HSP quantitatively account for the cohesion energy (density). An experimental latent heat of vaporization has been considered much more reliable as a method to arrive at cohesion energy than using molecular orbital calculations. Indeed, the goal of such extensive calculations for polar and hydrogen bonding molecules should be to accurately arrive at the energy of vaporization.

## MATERIALS AND METHODS

### Materials

Orlistat was procured from Intas Pharma Ahmadabad. All the other chemicals and solvents were analytical grade procured from Merck (India) and Molychem, Mumbai (India).

### Theoretical prediction of solubility

a. Fedor's Method/Fedor's Substituent constants

$$\delta = \sqrt{\frac{\sum \Delta\Delta U}{\sum \Delta V}} \tag{9}$$

Where,
*$\Delta\Delta$U is constant for energy mixing
**$\Delta$V is constant for molar volume.

b. Hoy's method/Hoy's molar attractions
According to [(cal cc) 1/2 $mol^{-1}$] unit

$$\delta = \frac{\Sigma \text{ molarattraction}}{V} \tag{10}$$

c. Van Krevelen's solubility parameters
The calculation of solubility parameter and molar volume van Krevelen's method, which is based on experimental molar volume measured $cm^3mol^{-1}$

$$\delta d = \Sigma Fd/V \tag{11}$$

$$\delta p = \sqrt{\sum Fp2/V} \tag{12}$$

$$\delta h = \sqrt{\sum Uh/V} \tag{13}$$

$$\delta 2T = \sqrt{\delta d2+\delta p2+\delta h2} \tag{14}$$

### Theoretical screening and comparison of orlistat by 3D parameter

Comparison of coformers and excipients was done by theoretical calculations and was selected on the basis of Krevelen's and Greenhalgh which the difference was calculated and selection of coformers was done. Solubility parameters for dry solutes may be obtained by group contribution methods. Calculations using Fedor's substituent constants [Tables 1 and 2], Hoy's molar attraction constants [Tables 3 and 4], and Van Krevelen constants [Tables 5-7] are the currently used methods. In the present investigation, these methods were employed to arrive at the solubility parameter values.[16,17]

**Table 1:** Calculation of ∂ value of orlistat by F, G, C method

| Fragments/groups | Number of groups | ΔΔU*for each (cal.mol$^{-1}$) | Total ΔΔU | ΔV** for each (m$^{-1}$ mol$^{-1}$) | Total ΔV |
|---|---|---|---|---|---|
| -$CH_3$ | 4 | 1125 | 4500 | 33.5 | 134 |
| -$CH_2$ | 18 | 1180 | 21240 | 16.1 | 289.8 |
| -C | 2 | 350 | 700 | 19.2 | −38.4 |
| -CH | 3 | 820 | 2460 | −1.0 | −3 |
| -NH | 1 | 1000 | 1000 | −9.0 | −9.0 |
| -O | 2 | 800 | 1600 | 3.8 | 7.6 |
| Ring closer | - | - | - | - | - |
| Conjugate bond | 3 | 400 | 1200 | −2.2 | −6.6 |
| | | | Σ=32700 | | Σ=37.44 |

**Table 2:** Theoretical prediction of cocrystal formation by Fedor's method

| Compound | δ value | Difference δ1-δ2 | Δδ | Possibility of cocrystal formation | |
|---|---|---|---|---|---|
| | | | | Krevelens Δδ ≤ 5MP | Greenhalgh Δδ ≤ 7MP |
| Orlistat | 9.76H | | | | |
| Sucrose | 6.31H | 9.76–6.31 | 3.45 | Yes | |
| Saccharin | 3.31H | 9.76–3.31 | 6.45 | Yes | |
| Succinic acid | 5.37H | 9.76–5.37 | 4.39 | Yes | |

**Table 3:** Calculation of solubility parameter of orlistat based on Hoy's molar attractions

| Fragments/group | Number of groups | ΔΔU*for each (calmol$^{-1}$) | Total ΔΔU | ΔV**for each (m$^{-1}$ mol$^{-1}$) | Total ΔV |
|---|---|---|---|---|---|
| -$CH_3$ | 4 | 148.36 | 593.44 | 21.548 | 86.192 |
| -$CH_2$ | 18 | 131.5 | 2.367 | 15.553 | 279.954 |
| -C=O | 2 | 262.96 | 525.62 | 17.265 | 34.53 |
| -CH | 1 | 85.99 | 85.99 | 9.557 | 9.557 |
| -NH | 1 | 180 | 180 | 8.774 | 8.774 |
| -O | 2 | 114.98 | 229.96 | 6.46 | 12.92 |
| CH=O | 1 | 117.12 | 117.12 | 13.417 | 13.417 |
| Six membered ring | 1 | −23.44 | −23.44 | 0 | 0 |
| Conjugated bond | 3 | 23.26 | 69.78 | 0 | 0 |
| Ortho | 2 | 9.69 | 19.38 | 0 | 0 |
| Meta | 2 | 6.6 | 13.2 | 0 | 0 |
| Base value | 0 | 0 | 0 | 0 | 0 |
| | | | Σ=4178 | | Σ=431.97 |

**Table 4:** Theoretical prediction of co-crystal formation by Hoy's method

| Compound | δ value | Difference δ1-δ2 | Δδ | Possibility of formation | |
|---|---|---|---|---|---|
| | | | | Krevelens Δδ ≤ 5MP | Greenhalgh Δδ ≤ 7MP |
| Orlistat | 9.67H | | | | |
| Sucrose | 15.31H | 9.67–15.31 | 5.64 | YES | |
| Saccharin | 15.53H | 9.67–15.53 | 5.86 | YES | |
| Succinic acid | 15.13H | 9.67–15.13 | 5.76 | YES | |

**Table 5:** Calculation of solubility parameter and molar volume of orlistat by Van Krevelen's solubility parameter

| Fragments/Groups | Number of groups | Fd | Total Fd | Fp | Total Fp | Fp2 | Uh | Total Uh |
|---|---|---|---|---|---|---|---|---|
| $-CH_3$ | 4 | 420 | 1680 | 0 | 0 | 0 | 0 | 0 |
| $-CH_2$ | 18 | 270 | 4860 | 0 | 0 | 0 | 0 | 0 |
| -C=O | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| $-CH_2$ | 1 | 80 | 80 | 0 | 0 | 0 | 0 | 0 |
| -NH | 1 | 280 | 280 | 610 | 610 | 372100 | 8400 | 8400 |
| -O | 2 | 100 | 200 | 410 | 820 | 672400 | 3000 | 3000 |
| -CH=O | 1 | 200 | 1800 | 0 | 0 | 0 | 0 | 0 |
| 6/5 member ring | 1 | 190 | 190 | 0 | 0 | 0 | 0 | 0 |
| | | | 8890 | | Σ=1044 | | | Σ=14400 |

**Table 6:** Theoretical prediction of cocrystal formation by van krevelen method

| Compound | δ value | Difference δ1-δ2 | Δδ | Possibility of formation | |
|---|---|---|---|---|---|
| | | | | Krevelens Δδ ≤ 5MP | Greenhalgh Δδ ≤ 7MP |
| Orlistat | 9.67H | | | | |
| Sucrose | 6.40H | 9.67–6.40 | 3.27 | YES | |
| Saccharin | 2.00H | 9.67–2.00 | 7.67 | YES | |
| Succinic acid | 7.18H | 9.67–7.18 | 2.49 | YES | |

### Preparation of spray dried cocrystals

Accurately weighed quantities of drug (orlistat), coformer (succinic acid, saccharin sodium, and sucrose), and carrier (maltose dextrin) in the ratio of 1:1:1 (100:100:100) and batches were prepared up to the ratio of 1:5:5 mg and were dissolved in solvent and cosolvent as ratio of 70:30 mL (water and ethanol) were prepared. 15 batches were passed through the spray dryer for the final product, and percentage yield and drug content was calculated.[18]

### Evaluation of cocrystals of orlistat

#### *Flow properties of orlistat cocrystal*

The prepared cocrystals were evaluated for flow properties such as angle of repose, flow rate (g/s), bulkiness, loose bulk density, porosity (%), and (%) compressibility.[19,20]

### Solubility determination

The solubility of orlistat was determined in mixed solvents as well as individual solvents. About 10 ml of the solvent blend was introduced into the 25 ml volumetric flask containing excess orlistat. The flasks were agitated in a constant temperature reciprocating shaker bath at room temperature (25±1°C) for at least 72 h to obtain equilibrium. Preliminary studies showed that this period was sufficient to ensure saturation at 25°C. After 72 h of equilibrium, aliquots were withdrawn, filtered (0.22 µm pore size), diluted, and analyzed at 215 nm on Shimadzu ultraviolet (UV)/V is spectrophotometer [Figure 1].[21,22]

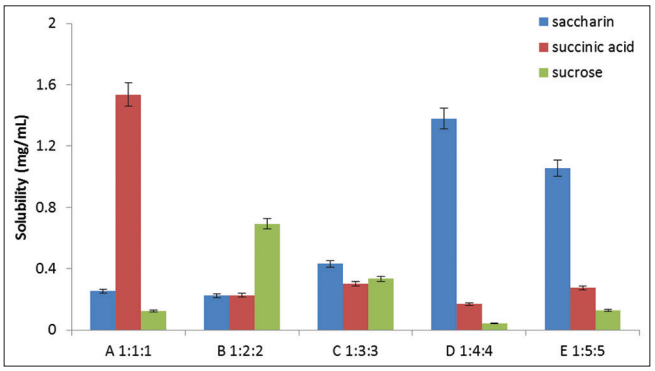


**Figure 1:** Saturated solubility of spray dried orlistat with different conformers

### Yield

Yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of the appropriate method of production.[23] Spray dried powdered was collected and weighed to determine % yield (PY) from the following equation [Figure 2].

$$Y(\%) = \frac{\text{Practical mass (spray dried powder)}}{\text{Theoretical mass (drug+coformer)}} \times 100$$

### Drug content

Spray dried powder equivalent to 100 mg of orlistat was weighed accurately and dissolved in the 100 mL of ethanol. The solution was filtered, diluted suitably and drug content was analyzed at 215 nm by UV spectrophotometer.[24] The

**Table 7:** Difference between δ1 and δ2 of orlistat and different types of coformer

| Drug and coformer | δ value | Difference δ1-δ2 |
|---|---|---|
| Orlistat | 9.67 H | |
| Cinnamic acid | 33.24 H | 23.57 |
| Citric acid | 21.28 H | 11.61 |
| Sucrose | 14.52 H | 4.85 |
| Saccharin | 13.07 H | 3.4 |
| Succinic acid | 15.13 H | 5.46 |
| Oxalic acid | 20.77 H | 11.1 |
| Malic acid | 22.60 H | 10.93 |
| Stearic acid | 9.14 H | −0.53 |

actual drug content was calculated using the following equation as follows Figure 3.

$$\%\ \text{Durg content} = \frac{\text{Actual amount of drug spray dired powder}}{\text{Therotical amount of drug indried powder}} \times 100$$

### *In vitro* dissolution study

*In vitro* dissolution studies of solid-state forms of orlistat were performed using eight-station USP Type II dissolution rate test apparatus. The accurately weighed samples equivalent of 100 mg of drug was used. The dissolution profiles of orlistat were determined in 900 ml of simulated gastric fluid 1.2 pH. Dissolution medium was kept in a thermostatically controlled water bath, maintained at 37±0.5°C at a rotation speed of 100 rpm. Samples were withdrawn periodically, and fresh equal volume of dissolution media was introduced in vessels to maintain the sink condition. Samples were filtered through Whatman filter paper, diluted and analyzed at 215 nm using Shimadzu UV-1800 Japan, spectrophotometer [Figures 4-6].[25-27]

### Solid characterization of cocrystals

### *Fourier transform infrared spectroscopy (FTIR)*

The FTIR spectra of orlistat and its cocrystals were determined using FTIR (Cary-60 ATR), spectra were recorded on a Cary-60 ATR. FTIR spectrometer in the range of 4000–400 $cm^{-1}$, [Figure 7] study was conducted to detect any changes on chemical constitution of the FNO and its coformers.[28,29]

### Powder X-ray powder diffraction (PXRD)

The XRD patterns of pure drug and the optimized crystals formulation were recorded using Philips analytical XRD (Model: PW 3710) (Philips, Almelo, The Netherlands) with a copper target over the interval of 5–70° $2\theta^{-1}$. The conditions were voltage 40 kV, current 30 mA, scanning speed 20/min,

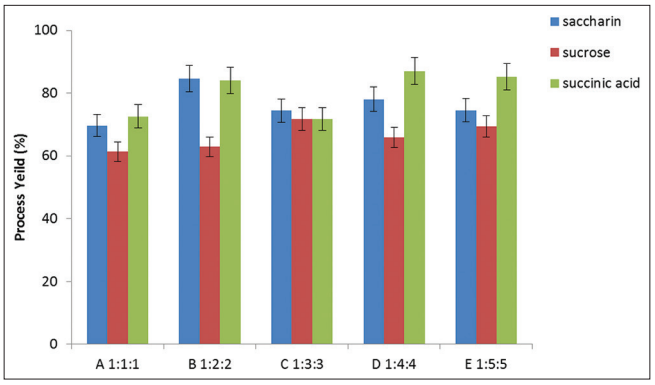


**Figure 2:** Percentage yield of spray dried orlistat formulation with conformers

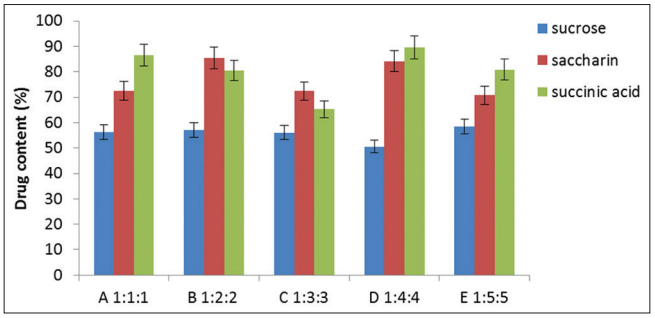


**Figure 3:** Drug content of spray dried formulation

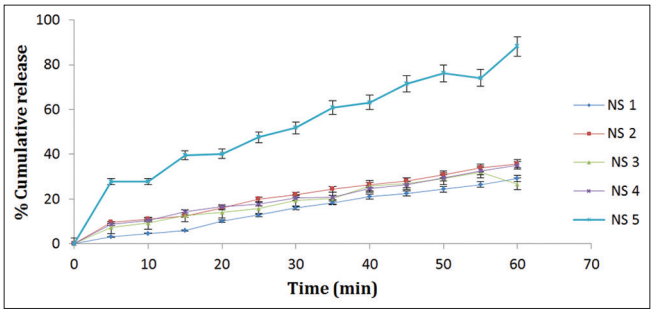


**Figure 4:** The % cumulative drug release of spray dried orlistat saccharin cocrystal

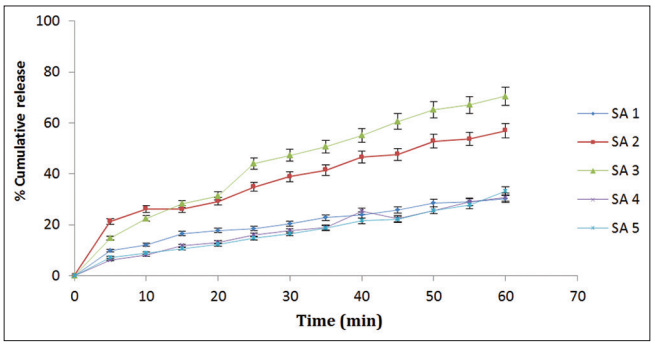


**Figure 5:** The % cumulative drug release of spray dried orlistat succinic acid cocrystal

and temperature of acquisition: Room temperature; detector: Scintillation counter detector; sample holder: Non-rotating holder [Figure 8].[30,31]

### Differential scanning calorimetry (DSC)

DSC was performed using DSC-60A (Shimadzu, Tokyo, Japan) calorimeter to study the thermal behavior of drug alone and prepared cocrystals. The samples were heated in hermetically sealed aluminum pans under nitrogen flow (30 ml/min) [Figure 9] at a scanning rate of 100°C/min from 500°C to 3000°C.[32,33]

### Scanning electron microscopy (SEM)

The outer macroscopic structure of the orlistat and cocrystals was investigated by SEM with a FEI Sirion-200 SEM (FEI, the Netherlands), operating at 10 kV [Figure 10]. The sample was fixed on a SEM-stub using double-sided adhesive tape and then coated with a thin layer of gold.[34,35]

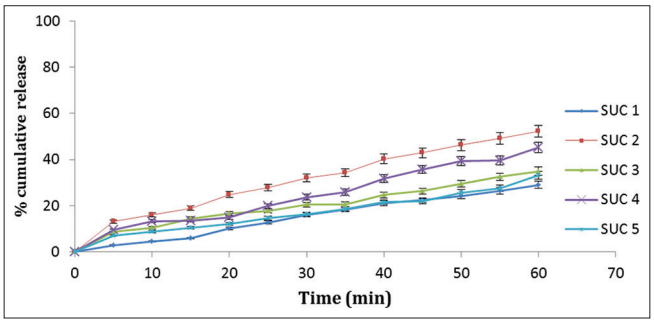


**Figure 6:** The % cumulative drug release of spray dried orlistat sucrose cocrystal

### Proposed structures of cocrystals

The proposed structures of cocrystals were developed using ChemSketch software. The thorough understanding of the structure of API and cocrystal formers is required to correctly locate the hydrogen bonding sites [Figure 11].[36,37]

## RESULTS AND DISCUSSION

### Theoretical prediction of solubility

#### *Fedor's substitution constants*

Fedor's proposed a method of determining solubility parameter without using the density value of the compound. This method is supposed to be better than small's method for two reasons: The contribution of much larger number of functional groups has been evaluated, and the method requires only the knowledge of structural formula of the compound [Table 1]. The following equation is used for directly determining (δ).[38]

$$\left[\delta = \frac{\sum i\Delta ei}{\sum i\Delta vi}\right]^{1/2}$$

Where Δei and Δvi are the additive atomic and group contribution for the energy of vaporization and molar volume, respectively [Table 2].[39]

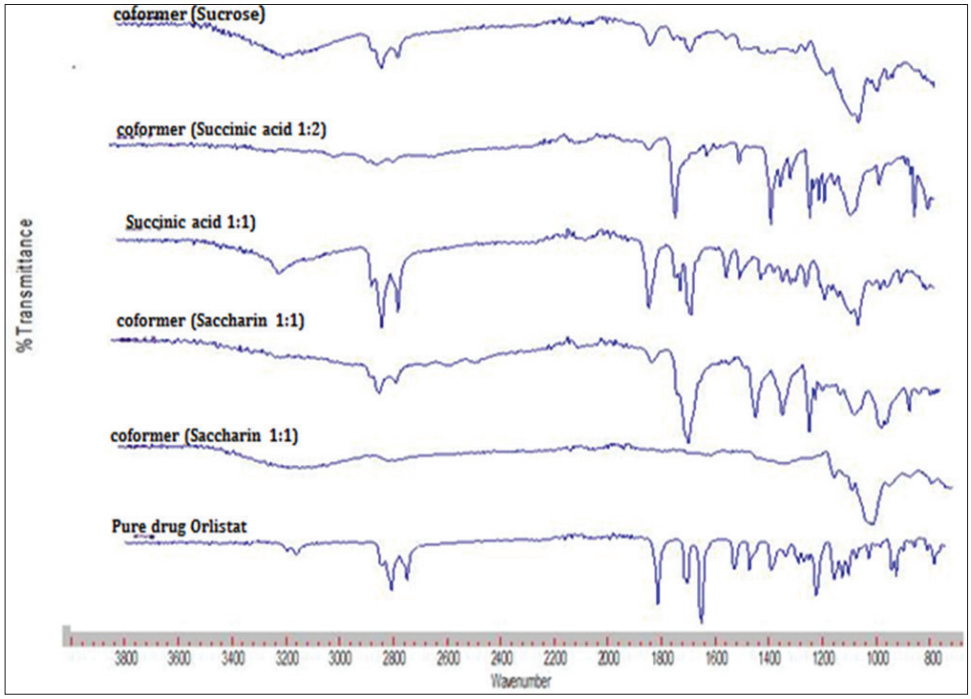


**Figure 7:** Comparative Fourier transform infrared pattern of orlistat and cocrystals using different coformer and ratios orlistat, saccharin 1:1, saccharin 1:2, succinic acid, and sucrose

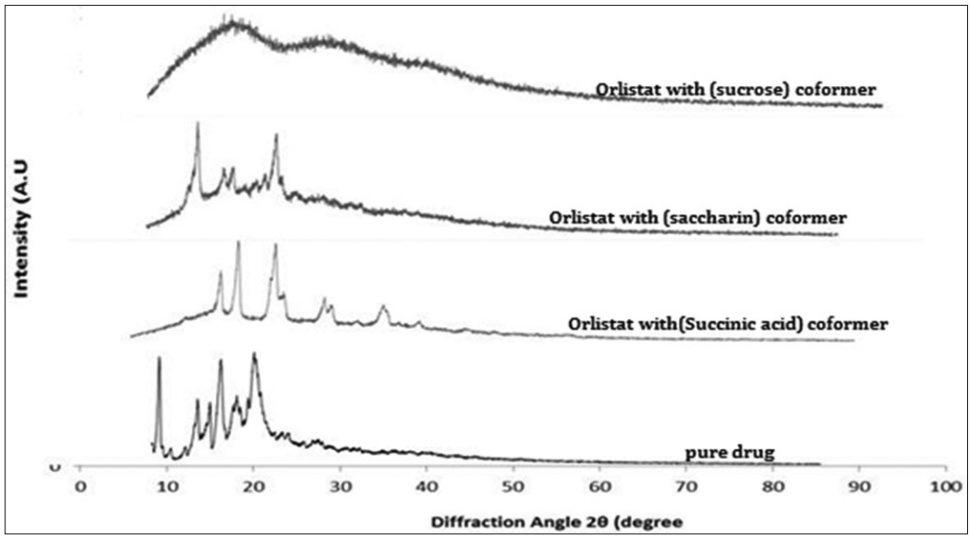


**Figure 8:** Overlay of comparative powder X-ray powder diffraction diffractograms of orlistat and prepared spray dried powder using three different coformer succinic acid; saccharin and sucrose

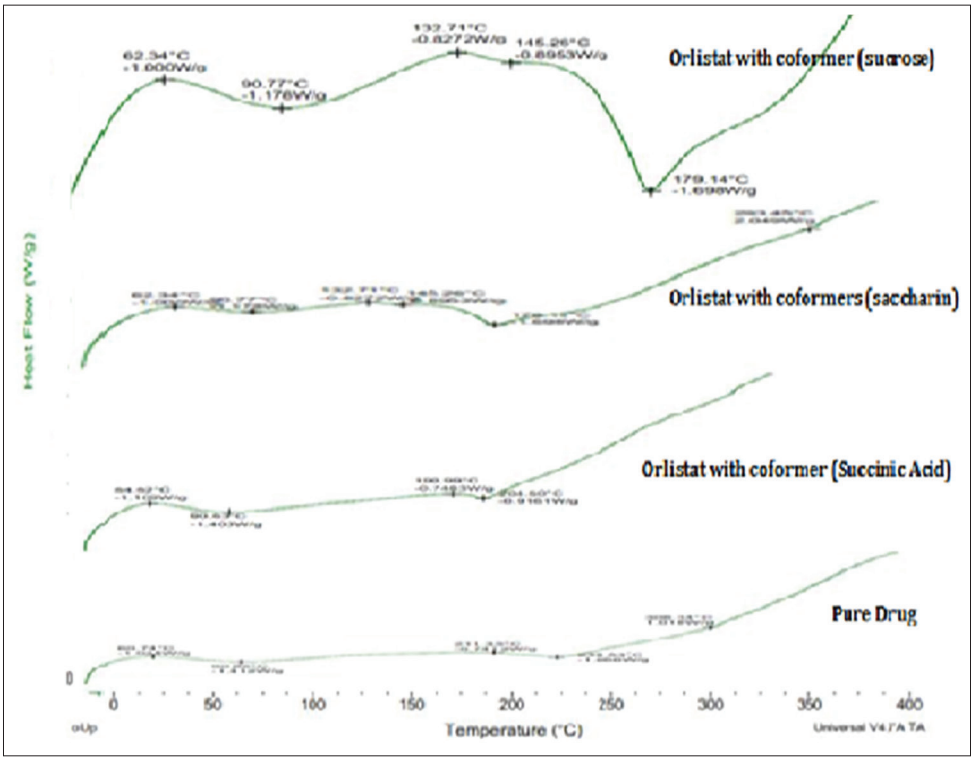


**Figure 9:** Differential scanning calorimetry thermogram of orlistat and prepared spray dried cocrystals using three different coformer succinic acid; saccharin and sucrose

### Hoy's method

Small's scheme has offered a convenient method for estimating the SP value for many solvents and polymers. However, the list of the constants is incomplete. Hoy published more group molar attraction constants derived from measurement of vapour pressure of a wide variety of groups [Table 3].[40] Solubility parameter (δ) is calculated from the following equation:

cf - density xΣFi/molecular weight

Where is the ΣF sum of the group molar attraction constants of the compound Hoftyzer and Van Krevelen published a series of group molar attraction constants similar to small and Hoy [Table 4].

### Van Krevelen's method

Van Krevelen derived Fi values for the contributions of atoms, i.e., C, H, N, 0, halogens, and constitutional effects (such as

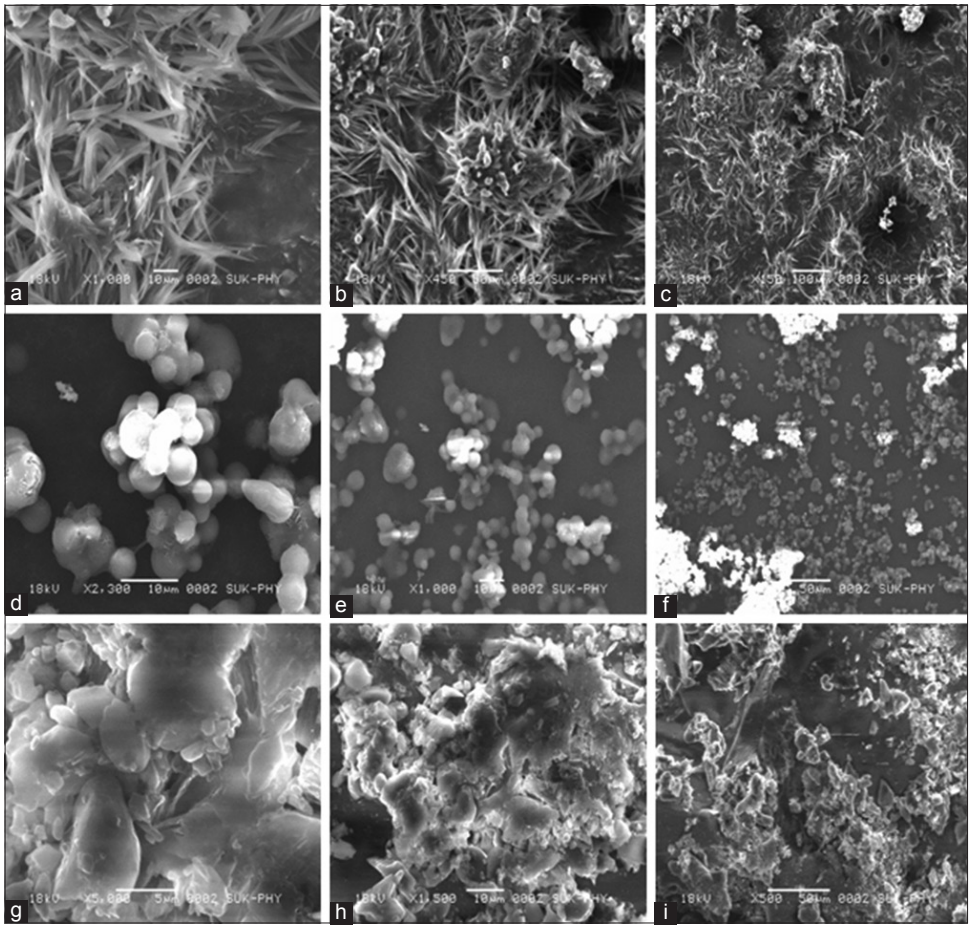

**Figure 10:** Microphotographic images of sucrose (coformer) with orlistat (a-c) (×1,000; ×450; ×150), saccharin (coformer) with orlistat (d-f) (×2,300; ×1,000; ×450), succinic acid (coformer) with orlistat (g-i) (×5,000; ×1500; ×500)

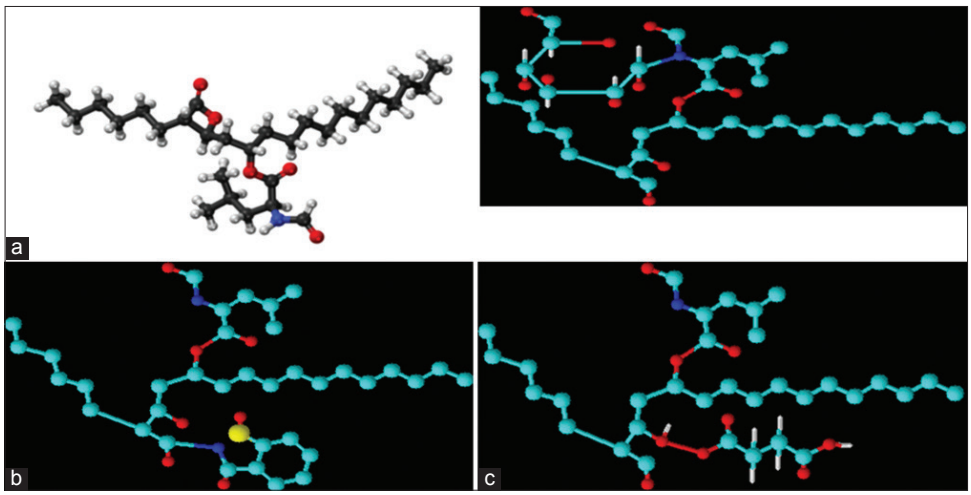

**Figure 11:** Proposed 3D structure of orlistat with coformer (a) sucrose (b) saccharin (c) succinic acid

double or tribal bonds) [Table 5].[41] Solubility parameter (δ) can be calculated using the following equation:

$$\delta = \frac{\sum Fi}{Vm}$$

Where, Σ = Fi, is the sum of the atomic contribution and Vm is molar volume [Table 6].

## Preparation and evaluation of orlistat cocrystal

### *Spray drying*

Effect of aspirator rate, spraying air flow pressure and inlet temperature on moisture content of product was determined. Percentage yield, effect of aspirator rate and spraying air flow pressure on % yield was graphically shown in Figure 2, and

their individual and combined effects on yield of the product are found to be 74.5%, 69.4%, and 85.2%, respectively; which was calculated. This indicated that aspirator rate was the major parameter affecting product yield. Spray drying process was optimized for aspirator rate, spraying air flow pressure and inlet temperature and its effect on drug content of the product, percentage yield was studied. Above mentioned optimized parameters were selected as it was observed that aspirator rate alone affected yield and drug content.[6,42]

### Flow properties of orlistat cocrystal

The angle of repose for all preparation fell within the range of 25–300 indicating good flow properties. The angle of repose is a characteristic of internal friction or cohesion of the particles. If the value of angle of repose is high crystals is cohesive and low crystals is noncohesive. There is a relationship between the angle of repose and the ability of crystals to flow.[43-45] The angle of repose should be in between 25 and 300 for good flow properties of crystals. The bulk density of a crystal depends primarily on particle size distribution, particle shape and the tendency of particle to adhere together. The orlistat showed good flow properties while the prepared cocrystals showed excellent flow properties. This indicates that the cocrystals improved the flow properties of orlistat.

### Saturated solubility

Figures summarize the experimentally determined solubility of orlistat in ethanol solution. The prepared cocrystals with coformers such as sucrose, succinic acid, and saccharine were shows significantly higher solubility compared to their cocrystals and drug alone. It is to be expected that orlistat would be solubilized well in cocrystal form due to reduction in crystallinity of drug and hydrogen bond formation between drug and conformer.[46] The cocrystals prepared by spray drying methods show a significant rise insolubility of orlistat [Figure 1]. Saturated solubility of succinic acid at point A1:1:1 shows 1.536 as it increases at A point, but shows low solubility at other points, whereas the saccharin at the point D shows 1.38 and E shows 1.054 (mg/mL) but varies at another point whereas the sucrose shows the low saturated solubility in all ratios.

### Percentage yield

Percentage yield of the succinic acid shows 87.1% at point E, and saccharin shows 84.62% whereas sucrose coformers shows the minimum percent yield shows 71.7% where saccharin shows the optimized yield [Figure 2].

### Drug content

Cocrystals are prepared by spray drying method; it involves inclusion of solvent. However, drug content analysis was performed on cocrystals prepared spray drying method in triplicate.[47] The orlistat content in the prepared cocrystals showed in range of 54–89% [Figure 3]. Drug content of succinic acid shows 89.6% where saccharin shows the 85.55% and is considered as the optimized batch from other coformers whereas sucrose shows minimum percent drug content in all ratios.

### *In vitro* drug release

The *in vitro* dissolution profiles of the cocrystals were compared with that pure orlistat. The *in vitro* dissolution rate of all prepared cocrystal was increased compared to the drug. Pure drug shows 31% drug release after 100 min, whereas, cocrystals prepared with coformer saccharin, succinic acid, and sucrose by spray drying shows 89.2%, 71.14%, and 48.10% after 100 min, respectively [Figures 4-6]. The high dissolution rate of prepared cocrystals can be attributed to decrease in crystallinity of orlistat due to interaction with coformer. The coformer saccharin produces small, uniform and stable orlistat cocrystal with markedly enhanced dissolution rate due to an increased solubility that is attributed to partial amorphization of the drug with increased surface area and improved wettability.[48]

### Solid state characterizations of orlistat cocrystals

#### *FTIR spectroscopy*

The possible interaction between the drug and the cocrystal formers was studied by FTIR spectroscopy. From the results of FTIR, it was observed that all the important peaks due to functional groups of drug were present in the cocrystals along with some new peaks. The result revealed considerable changes in the IR peaks of orlistat in prepared cocrystals when compared to pure drug thereby indicating the presence of hydrogen bonding had occurred in the cocrystals [Figure 7].[10] Specific 3301.300 OH stretching hydrogen bond 2918.302 C-H stretching alkanes group 2853.553 C-H stretching of alkanes group 1721.653 C=O stretching of carboxylic group 1665.0 C=C stretching of amides 1201.904 C-O stretching of alcohols 1841.144 C=O stretching of anhydrides shows peaks, respectively.

### Crystalline state evaluation: PXRD analysis

The XRD scan of pure orlistat showed intense peaks of crystallinity at 17.71°, 27.30, 29.400, 31.310, 33.400, and 46.220 (2θ) with peak intensities of 700, 1000, 1200, 1500, 2300, and 2800, respectively, indicating its crystalline nature [Figure 8]. Crystallinity was determined by comparing representative peak heights in the diffraction patterns of the cocrystals with those of reference. The relative degree of crystallinity (RDC) of orlistat in cocrystals was calculated according to the equation RDC= Isam/Iref, whereas Isam is the peak height of the sample under investigation and Iref is

the peak height at the same angle for the reference with the highest intensity.[49,50] The newly formed cocrystals showed the same 2θ but with lower intensities, also the presence of some new peak for coformer.

### DSC

DSC was conducted to indicate the molecular dispersion of orlistat into coformer. DSC thermograms are obtained for orlistat, succinic acid, and sucrose, and saccharine. DSC curves of pure drug and formulations were compared [Figure 9]. DSC revealed complex structure of solid crystals. Pure orlistat has showed well defined endothermic peak (Tm) at 50.98°C corresponding to the melting point of crystalline drug. The prepared cocrystals showed crystal in melting point, in prepared succinic acid, and sucrose and saccharine showed endothermic peaks at 94.07°C, 99.72°C, and 90.44°C, respectively.[8,50]

### SEM

The shape and surface morphology of the spray dried products was examined and investigated. The surface morphology studies revealed that the solid dispersion was closely compacted into small spherical form. Orlistat existed in exhibited flat broken needles of different sizes, with well-developed edges consisted of large crystalline particles of rather an irregular size the solid dispersions appeared in the form of spherical particles and the original morphology of components. These results demonstrated that orlistat in solid dispersion was homogeneously dispersed into carriers and coformers at the molecular level showed spherical particles with wide particle size distribution uniform spherical and porous particles with similar particle morphology and size [Figure 10].[39,50] Crystals of bigger size and regular shape with an apparently smooth surface characterized the pure drug. Figure 10 shows microphotographs of orlistat and prepared cocrystals, from that it was observed that orlistat showed large crystals while cocrystals prepared by spray drying method showed small, uniform crystals.[50] Cocrystals of other methods showed reduced crystallinity as compared to pure orlistat.

### Proposed structure with copolymer

The characterization results of drug and all cocrystals enable one to determine the possible structures of newly formed cocrystals using the concept of hydrogen bonding [Figure 11]. The chloride ion is one of the most preferred anions for salts of cationic APIs. It has been estimated that approximately half of the salts of cationic drugs are marketed as hydrochloride salts. The exceptional ability of the chloride ion to act as hydrogen bond acceptor is the key to the approach. In addition, chloride ions may form hydrogen bonds to weaker, neutral hydrogen bond donors available in the system. These neutral donors play a role in the chloride coordination sphere. For example, when a stronger donor is not available, the ubiquitous C-H donors will often occupy available acceptor sites on the chloride ion. In systems with only a few strong hydrogen bond donors, the hydrogen bond accepting ability of the chloride ion will often be underutilized, and the addition of another strong hydrogen bond donor guest molecule can be accommodated, often by displacing one of the weaker C-H.....$Cl^-$ interactions. The possibility structure of orlistat drug with coformer, i.e., succinic acid, sucrose, and saccharine.

## SUMMARY AND CONCLUSION

The characterization of was done with melting point, FTIR spectroscopy and found to encompass with the specification. Percentage yield of the succinic acid shows 87.1% at saccharin shows 84.62% sucrose coformers shows the minimum yield. *In vitro* drug release in PBS 1.2 and showed 85–90% cumulative amount of drug release within period 0 and 60 min, respectively. Theoretical prediction of excipient's and coformers using Hansen solubility parameter was done. Solid dispersion technique found to be effective in increasing the aqueous solubility of orlistat. HSP was used from a selection of coformers. The selected coformer was based on HSP by which three methods are used such as Fedor's methods, van Krevelen's methods, and hoys methods. Based on their given value the selection of coformer was done by Krevelen's $\Delta\delta \leq 5$MP and Greenhalgh $\Delta\delta \leq 7$MP. Proposed structure of orlistat was developed using ChemSketch software. The thorough understanding of the structure of API and coformer is required to locate correctly the hydrogen bonding. Coformer selection was done based on hydrogen bonding in structure. The surface morphology studies revealed that the solid dispersion was closely compacted into small spherical form. These results demonstrated that orlistat in the solid dispersion was homogeneously dispersed into carriers and coformers at the molecular level showed spherical particles with wide particle size distribution (10–100 μm) but uniform spherical and porous particles were obtained with similar particle morphology and size.

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