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Der Pharmacia Lettre, 2010: 2 (1) 25-40
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Directly Compressible Roxithromycin recrystallized agglomerates by solvent change technique

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Abstract

In the present investigation, the enhancement of solubility, dissolution rate and other physicochemical properties of roxithromycin (RTM) were carried out by preparing the recrystallized agglomerates using solvent change technique with three solvents system. Based on the solubility of RTM in different organic solvents the best solvent (ethanol), non-solvent (distilled water) and bridging liquid (chloroform) were selected. The effect of different hydrophilic polymers like hydroxyl propyl methyl cellulose (HPMC), Polyethylene glycol (PEG) and polyvinyl pyrrolidone (PVP) were studied on the solubility, dissolution rate and other physicochemical properties. The optimized recrystallized agglomerates were evaluated for flowability, packability, wettability and compared to raw crystals of RTM. The agglomerates were also characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (XRPD), Fourier transforms infrared spectroscopy (FTIR) and scanning electron microscopy (SEM).The recrystallized agglomerates showed improvement in solubility, dissolution rate and other physicochemical as compared to RTM crystals. The optimized recrystallized agglomerates with HPMC showed good sphericity as well as improvement in *in vitro* drug release comparative to agglomerates with other hydrophilic polymers. The improved compaction properties of the agglomerated crystals were due to their fragmentation during compression. The DSC showed a decrease in the melting enthalpy indicating disorder in the crystalline content. The XRD also revealed a characteristic decrease in crystallinity.FTIR study revealed that no chemical changes in prepared recrystallized agglomerates. It was concluded that the used hydrophilic polymers can be employed to prepare recrystallized agglomerates for enhancing the solubility and dissolution rate of RTM.

Key words: Roxithromycin, solvent change technique, physicochemical properties, Recrystallized agglomerates, Packability, wettability.

Introduction

Developing novel methods to increase the bioavailability of drug substances that essentially have poor aqueous solubility is a great challenge to solid dosage form formulators. Mechanical micronization of crystalline drug substances, incorporation of surfactants during the crystallization process and solid dispersion are the techniques commonly used to improve the bioavailability of poorly water soluble drug substances [1-2].The micronization method was found to modify the flow and compressibility of crystalline powders and causes formulation related problems. Incorporation of surfactants generally less significant for aqueous solubility improvement.

To overcome these problems, Kawashima and their co-workers [3-5] developed a spherical crystallization technique that lead to improving the flow and direct compressibility of number of microcrystalline drug substances. Spherical crystallization was defined by Kawashima as "An agglomeration process that transforms recrystals directly into a compacted spherical form during the recrystallization process." It also enables co-precipitation of drug and encapsulating polymer in the form of spherical particle. Enhancement of dissolution profile was also achieved through recrystallization and agglomeration by using the spherical crystallization technique. This technique involved selective formation of agglomerates of recrystallized crystals held together by liquid bridges. Spherical crystallization technique has been successfully utilized for improvement of flowability and compressibility of crystalline drug, preparation of microsponges, microspheres and masking of the bitter taste of drug substances. This technique could enable subsequent process such as separation, filtration, drying to be carried out more efficiently. Furthermore the resultant recrystallized agglomerates could be easily compounded with other pharmaceutical powders and dosage form like tablets and capsules due to their spherical shape [6].

Direct tabletting of pharmaceutical materials is desirable to reduce the cost of tablet production [7].Conversely, directly compression of high-dosed drug requires good micromeritic properties such as flowability and reproducible compression behavior. Spherical crystallization technique transforms directly the fine crystals produced in recrystallization into a spherical shape. Recrystallized agglomerates exhibit improved properties like flowability and compressibility for direct tabletting or coating without further processing (like mixing, agglomeration, sieving etc.) [8-9].There is many active pharmaceutical agents in pharmaceutical industry with unfavorable flowability and compressibility properties due to irregular crystal habit. Poor compressibility of a specific crystal habit of drug can be attributed to the presence of crystal faces that gives poor adhesion to each other and absences of the faces that are required for optimal adhesion during compression process.

Most commonly used method of spherical crystallization are spherical agglomeration method (solvent change technique) and Quasi-Emulsion Solvent Diffusion technique (QESD) [10].In the Solvent change technique, a quasi-saturated solution of the drug substance in a solvent in which it is especially soluble, is poured into a poor solvent of the drug. The good and the poor solvents are freely miscible and interaction (binding force) between the solvents is stronger than drug interaction with the good solvent, therefore crystals precipitate immediately. A suitable amount of a third solvent, which is not miscible with the poor solvent and which preferentially wets the

precipitated crystals, is added to the system while stirring. This third solvent, called as 'bridging liquid', can collect the crystals suspended in the system by forming liquid bridges between the crystals due to capillary negative pressure and interfacial tension between the interface of solid and liquid [11]. The solvent change method has been applied to several drug substances to improve the physicochemical properties [12-13].When interaction between the drug and the good solvent is stronger than that of the good solvent and poor solvent, the good solvent drug solution is dispersed in the poor solvent, producing quasiemulsion droplets, even if the solvents are normally miscible. This is due to an increase in the interfacial tension between good and poor solvent. Then the good solvent diffuses gradually out of the emulsion droplet into the outer poor solvent phase. The counter-diffusion of the poor solvent into the droplet induces the crystallization of the drug within the droplet due to the decreasing solubility of the drug in the droplet containing the poor solvent.

Roxithromycin (RTM) is the first new generation macrolides. It is an acid stable, semi-synthetic 14-membered ring macrolide antibiotic, in which the erythronolide A lactone ring has been altered to prevent inactivation in the gastric environment. It has proven clinical efficacy against some *Staphylococcus spp*. and many *Streptococcus spp.* and also retains the appropriate anti-bacterial profile of the older macrolides.The antibacterial spectrum and excellent penetration into respiratory tissue and secretion has provided ethical justification of using Roxithromycin 300mg as "empirical" antibiotic of choice in Lower respiratory tract infection.

RTM is poorly soluble in water and the drug of choice for treatment of Cryptosporidiosis, a severe diarrheal condition in AIDS patients [14]. In vivo performance of conventional formulations of RTM was hampered by poor bioavailability due to poor solubility and low residence time under such adverse physiological conditions with very high peristaltic movement. To increase the oral absorption of RTM, it is important to improve the drug solubility in gastrointestinal tract, enabling rapid and complete absorption from the stomach. Thus RTM is a model drug for solubility and other physicochemical properties improvement studies. Hence, the improvement of aqueous solubility in such a case is a valuable goal to improve therapeutic efficacy. Spherical crystallization of Roxithromycin with Eudragit S100 and silica were prepared by the emulsion solvent diffusion method to mask the bitter taste of RTM but the aqueous solubility was not satisfactorily improved [15]. There are no reports available on the spherical crystallization of RTM by using hydrophilic polymer to improve aqueous solubility and dissolution rates in addition to improving its micrometric properties, and hence the present work has been undertaken with this objective.

In the present work, RTM was chosen model drug candidate as their irregular stone shaped forms exhibited poor micromeritic properties and they also had poor aqueous solubility. Novel solvent change technique was developed by incorporating different hydrophilic polymers like hydroxyl propyl methyl cellulose (HPMC), Polyethylene glycol (PEG) and polyvinyl pyrrolidone (PVP) during the agglomeration process. The agglomerates were evaluated by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), Fourier transforms infra red spectroscopy (FTIR) and scanning electron microscopy (SEM) for determining the chemistry, crystalline form and crystal habit of the prepared recrystallized agglomerates.

Materials and Methods

Roxithromycin was procured as a gift sample from Alembic Research center (Vadodara, India).Hydroxyl propyl methyl cellulose (HPMC) was supplied by Colorcon, (Goa, India).Polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP), Ethanol, Chloroform were purchased from S. D. Fine (Mumbai, India).

Method

All recrystallized agglomerates were obtained by the solvent change method using distilled water with different hydrophilic polymers (table 1) as an external phase. The internal phases consisted of a good solvent with drug substances and chloroform was used as bridging liquid. A certain amount of Roxithromycin (2-3 gm) was dissolved in 20mL of ethanol and kept under constant agitations in sonicator. The prepared roxithromycin saturated solution in good solvent was poured slowly in 200mL of distilled water (poor solvent) containing the different hydrophilic polymers under stirring rate at 1000 rpm. After five minutes the added RTM in good solvent was precipitated or recrystallized in poor solvent. Afterward 5mL of chloroform was added drop wise as bridging liquid to form bridges between the recrystallized particles and converted into agglomerated form within 30 minutes. The system was filtered to separate the recrystallized agglomerates from the preparation system. The resultant product was washed with distilled water and dried in an oven at 40^0C for 12 hr. The whole process was carried out at room temperature.

Table 1. Product codes of roxithromycin and prepared recrystallized agglomerates

Name of stabilizing agent	Recrystallized agglomerated Code
Roxithromycin	RTM
Hydroxy propyl methyl cellulose(HPMC)	RTM-HPMC
Polyethylene glycol(PEG-6000)	RTM-PEG
Polyvinyl pyrrolidone(Povidone K30)	RTM-PVP

Yield and drug content

The prepared recrystallized agglomerates were dried, weighed after drying and the production yield was calculated. Prepared agglomerates were powdered, from which powder equivalent to 20mg of roxithromycin were taken separately for study. It is then extracted with 80mL of 0.1N HCl through sonication for 20 minutes. Place few minute in refrigerator filter and adjust the pH in the range of 6-7 and make up the volume upto 100mL with distilled water. One micro liter form the above solution was diluted to 6mL with the distilled water in 10 mL volumetric flask to it added 0.7mL of Eosin Y solution (4×10^{-3} M), mixed well and then to it added 1 mL 0.4M acetate buffer (pH 3) adjusted the volume up to 10mL with distilled water. Finally the absorbance was measured spectrophotometrically (Pharma spec 1700, Shimadzu Corporation, Kyoto, Japan) at 545nm, against an appropriate blank prepared simultaneously [16].

Saturation solubility study

An excess amount of RTM and recrystallized agglomerates of RTM were added in screw capped test tubes with fixed volume (20 mL) of distilled water. The resulting suspension was treated at room temperature with 100 rpm in incubator shaker. Samples were withdrawn after 48 hrs and filtered through 0.2µ filters. Took 5 mL of filtrate from dispersion of above roxithromycin in water after 48 hr and diluted to 60mL with 0.1N HCl, adjusted the pH 6 to 7 by adding 0.4M NaOH solution and make up the volume up to 100mL with distilled water. 1mL form the above solution was diluted to 6 mL with the distilled water in 10 mL volumetric flask and to it added 0.7 mL Eosin Y solution (4 X 10-3 M), mixed well and to it added 1 mL 0.4M acetate buffer (pH 3) adjusted the volume up to 10mL with distilled water. The absorbance was measured spectrophotometrically at 545nm against an appropriate blank prepared simultaneously. Solubility of the recrystallized agglomerates in distilled water was determined either from the calibration graph or using the corresponding regression equation.

Flow properties

Flow properties of the RTM and recrystallized agglomerates of RTM were studied by determining the bulk density, tap density, Carr's Index and Hausner ratio and angle of repose by fixed funnel and free standing cone method.

Measurement of Packability

The packability of the recrystallized agglomerates was investigated by tapping the RTM and their recrystallized agglomerates into a 50-mL measuring cylinder using a tapping machine. Initially, 25 g of substance was weighed and then was gently poured into a measuring cylinder. The volume of 25 g samples was recorded. The poured density (minimum density) was calculated from the powder mass (25 g) and the volume. Then the cylinder was tapped and the volume was recorded after every 100 taps until the volume did not change significantly. The compressibility was evaluated by measuring the tapped density according to the modified Kawakita (1) and Kunos (2) equation.

$$N/C = 1/(ab) + N/a \qquad (1)$$

Where as $\{C = (Vo-Vn)/Vo,\ a = (Vo-V\infty)/Vo.\}$

N =Number of tapping, C =Difference in volume (degree of volume reduction.), a and b = constant for packability and flowability, Vo = Initial volume, Vn = Final volume after n^{th} tapping, $V\infty$ = Powder bed volume at equilibrium.

$$\rho_f - \rho_n = (\rho_f - \rho_o) \cdot \exp.(-kn) \qquad (2)$$

Where ρ_f, ρ_o, ρ_n are Apparent densities at equilibrium, nth tappeded, initial state respectively The compressibility was assessed by comparing the constants a, b, 1/b and k in equation 1 and 2 respectively. The constant a represents the proportion of consolidation at the closest packing attained and constant 1/b describes cohesive properties of powders or the apparent packing velocity obtained by tapping. The constant k in Kuno's eq. represents the rate of packing process [17].

Compressibility study by Heckel equation

The Heckel equation (8) is widely used for relating the relative density (D) of a powder bed during compression to the applied pressure (P).It is assumed that the densification of the powder columns follows a first order kinetics. Thus the degree of material densification is correlated to its porosity.

$$\text{Ln } [1/1\text{-}D] = K P + A \qquad (3)$$

Where as
D = Relative density of compact at pressure P.
K = Slop of the straight line portion.
A = Intercept of the straight line obtained by linear regression from the Heckel plot
Py = Mean yield pressure which is the reciprocal of K.

The slop of Heckel plot was intended to give a measure of plasticity of a compressed material. Greater slops indicated a greater degree of plasticity of material. The slop was also related to the yield strength (y) of the material by the equation.

$$K = 1/3\ Y.$$

The reciprocal of K to be the mean yield pressure (Py) in order to study whether the fragmentation of particles was the predominant compaction mechanism of compaction.

A constant A is a sum of two densification terms:

$$A = \text{Ln } [1/1\text{-}D0] + B \qquad (4)$$

Where
In [1/1-D0] = Related to the initial die filling
B= The densification due to the slippage and rearrangement of both primary and fragmented particles, before deformation and bonding of the discrete particles.

The constant A and B can be expressed as relative densities using

$$DA = 1 - e^{-A} \qquad (5)$$
$$D0 = 1 - e^{-A0} \qquad (6)$$
$$DB = DA - D0 \qquad (7)$$

Where
A = Intercept at given pressure
A0 = Intercept of line at P = 0
DB = The difference between the DA and D0 represented the extent of particle rearrangement which represent fragmentation property of the powder.
DA = Die filling and particle rearrangement which represent the total degree of packing at zero and low pressure.
D0 = Particle rearrangement during die filling which is related to the typical particle shape. Therefore it is the relative density of the powder bed at the point when the applied pressure equals zero.

It is used to describe the initial rearrangement phase of the densification as a result of die filling [18].

Wettability/ powder bed hydrophilicity study

The RTM and their prepared recrystallized agglomerates were placed above sintered glass disk forming the bottom of glass tube. Methylene blue crystals were placed above the powder sample. The whole device was brought into contact with water. Measure the time taken for the capillary rising of water to the surface so as to dissolve methylene blue crystals. Minimum is the time required to reach the water to surface maximum is its wettability [13].

In-vitro dissolution studies

The in vitro dissolution studies were carried out using eight station USP type II dissolution apparatus. The study was carried out in 900 mL of Acetate buffer pH 5.0 as dissolution medium. Dissolution medium was kept in a thermostatically controlled water bath, maintained at 37 ± 0.5^0C.The paddle was rotated at 100 rpm. At predetermined time intervals, 5mL of samples were withdrawn and assessed for drug release spectrophotometrically by using method above mentioned in saturation solubility study. The samples were assayed through ultraviolet absorbance measurement at 540nm using UV-Visible Spectrophotometer (Shimadzu UV-1700, Japan) by an analytically validated method (r^2 = 0.9992). To increase the reliability of the observations, the dissolution studies were performed in triplicate.

Fourier transforms infrared spectroscopy (FTIR)

FT-IR spectra of roxithromycin and recrystallized agglomerates were recorded on Shimadzu FTIR–8400 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400 – 4000 cm^{-1} at spectral resolution of 2 cm^{-2} and ratio against background interferogram. Spectra were analyzed by software supplied by Shimadzu.

Powder X-Ray Diffraction (PXRD)

Crystallinity of the drug and the samples was determined using the Philips Analytical XRD (Model: PW 3710, Holland) with copper target. The conditions were: 40 kV voltages; 30 mA current; at room temperature. The samples were loaded on to the difffractometer and scanned over a range of 2θ values form 2 to 50 ^{0} at a scan rate of 0.05 ^{0}/min.

Differential Scanning Calorimentry (DSC)

Thermal properties of the untreated drug and the prepared agglomerates were analyzed by DSC (TA Instruments, USA, and Model: SDT 2960). The samples were heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 30 to 200 ^{0}C at a heating rate of 10 ^{0}C/ min, using nitrogen as blanket gas.

Scanning Electron Microscopy (SEM)

The surface topography of the roxithromycin and recrystallized agglomerates was examined using scanning electron microscope (Jeol, JSM-5200, Japan, 15 KV). Samples were coated with gold film under vacuum using a sputter coater (SPI Sputter™ Coating Unit, SPI Supplies, Division of Structure Probe, Inc., PA, USA) and then investigated.

Results and Discussion

The study started with the choice of the best solvent for preparation of recrystallized agglomerates of RTM by solvent change technique. Ethanol was selected as good solvent in which the RTM was very soluble (0.45mg/mL). It was possible to obtain a very concentrated drug solution which increases the densification of the material during the crystallization process in ethanol. The concentration of the solution at room temperature corresponds to a quasi-saturated solution of roxithromycin in ethanol. The crystallization of roxithromycin from ethanol, gave needle-shaped crystals. The addition of the solution to the non-solvent dispersion phase (distilled water) caused RTM precipitation and a weak tendency to particle agglomeration. The addition of the bridging liquid (chloroform) favored the transfer of the drug to this emulsified phase in which crystal agglomerates densified and developed spherical recrystallized agglomerates.

Production yield and drug content

The production yield of the prepared recrystallized agglomerates by solvent change technique was found to be above 80 % (Table:2) which was calculated by measuring the weight of the prepared recrystallized agglomerates by considering the raw material taken for the spherical crystallization as 100.0%. The production yields of recrystallized agglomerates by solvent change technique were on lower side i.e. 80-90%.The RTM content in all recrystallized agglomerates was found to be above 90%. The content in the prepared recrystallized agglomerates was in the range of 92-94% as mentioned in table: 3 which are lower than that of raw crystals of RTM. The lower content of prepared recrystallized agglomerates might be due to loss of 5-6% CBZ during processing. The reason for loss of drug may be due to sticking of drug to the walls of the beaker or to the stirrer shaft. Another reason for loss of drug may be due to solubility of recrystallized agglomerates in dispersed system and filtered.

Saturation solubility

The solubility study was carried out in distilled water for both RTM and their recrystallized agglomerates with different hydrophilic polymers. Solubility in distilled water were for RTM (0.267 ±0.006 mg/mL), and recrystallized agglomerates RTM-HPMC (0.510 ±0.015 mg/mL), RTM-PEG (0.428 ±0.014 mg/mL), and RTM-PVP (0.325 ±0.012mg/mL). There is significant improvement (** $P<0.01$) in the solubility of recrystallized agglomerates in distilled water compared to raw RTM crystals as shown in table: 2. The improvement in solubility of recrystallized agglomerates may be due to changes in the crystal forms because of different crystal habit, structure, surface modification and in some instances solvents included into the crystals forming solvets or clathrates. The changes in the surface properties and the reactivity of drug particles and internal energy of the molecules play important role to increase solubility.

Density and flowability study

Tables 2 shows the bulk and tap density of the agglomerated crystals, the results indicated that both densities of the agglomerated crystals showed on lower side because of the increase in volume and porosity of agglomerated crystals. Flowability parameters (Table 2) of the RTM and optimized recrystallized agglomerated crystals were determined in term of Angle of repose, Carr index and Hausnar ratio. Recrystallized agglomerated crystals were found to have significantly lower angle of repose (** $P<0.01$) in comparison to the raw crystals of roxithromycin ,which

could be due to the irregular stone shaped crystals of roxithromycin that is reflected from SEM (Fig.6) hindered in the uniform flow of crystals from funnel. The Carr index revealed that the flowability of the RTM was significantly poor (** P<0.01) than that of the agglomerated crystals i.e. these agglomerates have lower Carr index than raw crystals. Hausnar ratio of agglomerated crystals was also less than raw crystal indicating improvement in flowability of agglomerated crystals. The RTM have higher bulk density and thus lower porosity as compared to the prepared recrystallized agglomerates. The lower density is likely to be related to the intraparticle porosity or particle density and hence the reduction in bulk density of the recrystallized agglomerated samples indicates a greater porosity within the agglomerated particles. The excellent flowability of recrystallized recrystallized agglomerates comparative to raw crystals of roxithromycin may be due to significant reduction in interparticle fraction because of their agglomerated spherical shape with reduction in the surface area.

Packability study

Packing process of the recrystallized agglomerates in a measuring cylinder by tapping was described by Kawakitas and Kunos equation. The packing ability was assessed by comparing the constants **a, b** and **k** in Kawakitas and Kunos equation (table: 2).The constant **a** for the recrystallized agglomerates was smaller than the raw crystals of RTM. This indicated that the recrystallized agglomerates were easily packed, even without tapping. The larger **b** values of the recrystallized agglomerates proved that the packing velocity of the recrystallized agglomerates by tapping was slower than that of the crystals which are not agglomerated. The smaller **k** in kuno equation for the recrystallized agglomerates coincides with the above findings. The packability improvement of recrystallized agglomerates may be due to lower surface and wider particle size distribution of spherical crystals, during tapping process smaller particle might have infiltrated into the voids between the larger particles and resulted in improved packability.

Powder bed hydrophilicity study

Table 2 indicates results of powder bed hydrophilicity study of RTM and prepared recrystallized agglomerates.The recrystallized agglomerates showed significantly shortest rising time (** P<0.01) of water to its surface compared to the raw RTM crystals represent better wattability of prepared recrystallized agglomerates as compared to raw RTM. The order of wettability was RTM-HPMC > RTM-PEG > RTM-PVP >RTM.The reason for superior wettability of recrystallized agglomerates may be due to the presence of hydrophilic polymers on the recrystallized RTM.

Compressibility study

The recrystallized agglomerates showed higher DB value (table 3 and Figure 1) .This implies that the agglomerates show more extensive particle rearrangement compared with the raw crystals of roxithromycin. At lower compression pressure the large agglomerates were fractured into small ones, which facilitate the further rearrangement. At lower compression pressure the rearrangement and crushing of recrystallized agglomerates proceeds simultaneously and at higher compression pressure fractured crystal particles are cohered and bounded with one another while undergoing plastic deformation.D0 values represent the degree of initial packing in the die as result of die filling. The prepared agglomerates had the higher D0 value because of higher degree of packing in the die.DA values represent the total degree of packing at zero and low pressure, the value is on higher side for recrystallized agglomerates. Higher values of D0

represent the better initial packability in a die while the higher value of DA represent densest packing rearranged and fractured particles into a die. The slope of the heckel plot (k) is an indicative of plastic behavior of the powder material. A larger slop is related to a greater amount of plasticity in the material. The mean yield pressure is related inversely to the ability of a material to deform plastically under pressure.

Table 2. Evaluation parameters of RTM and prepared recrystallized agglomerates with different polymers

Name of parameters	Product Code			
	RTM	RTM-HPMC	RTM-PEG	RTM-PVP
Product yield (%)*	NA	85 ±2.137	82 ±1.898	90 ±1.482
Drug content (%) *	97 ±1.638	94 ±2.366	92 ±3.563	93 ±2.363
Saturation solubility(mg/mL)*	0.267 ±0.016	0.510 ±0.015	0.428 ±0.014	0.325 ±0.012
Bulk density(gm/mL)*	0.565 ±0.075	0.285 ±0.066	0.295 ±0.055	0.305 ±0.064
Tap density(gm/mL)*	0.715 ±0.012	0.335 ±0.024	0.345 ±0.042	0.365 ±0.056
Compressibility index*	22.1 ±0.568	14.9 ±0.789	14.5 ±0.159	16.4 ±0.357
Hausnar ratio*	1.283 ±0.456	1.175 ±0.248	1.169 ±0.359	1.197 ±0.537
Angle of repose *	40 ±2.569	26 ±1.568	22 ±2.468	24 ±1.569
Wettability study* Water rising time(hrs)	20 ±0.896	10 ±0.986	12 ±0.789	14 ±0.458
Packability parameters from Kawakita and Kuno equation.				
a	0.536	0.194	0.214	0.227
b	0.0014	0.0119	0.0049	0.0070
k	0.0146	0.0036	0.0043	0.0030

* Each value represents mean ± S.D. (n = 3)

Table 3. Heckel plot parameters of roxithromycin and recrystallized agglomerates

Product Code	RTM	RTM-HPC	RTM-PVP	RTM-SSG
Slope*	0.0262 ±0.0025	0.0292 ±0.0017	0.0303 ±0.0021	0.0314 ±0.0032
Myp*	38.12 ±1.2352	34.20 ±1.6255	32.98 ±1.4584	31.90 ±0.9867
A*	0.6398 ±0.0089	0.7696 ±0.0098	0.7180 ±0.0067	0.7886 ±0.0095
A0*	0.6202 ±0.0125	0.7108 ±0.0068	0.6719 ±0.0088	0.7523 ±0.1242
D_{A*}	0.4726 ±0.0058	0.5368 ±0.0086	0.5123 ±0.0068	0.5457 ±0.0096
D_{0*}	0.4622 ±0.0152	0.5088 ±0.0088	0.4893 ±0.0097	0.5287 ±0.0086
D_{B*}	0.0104 ±0.0065	0.0281 ±0.0046	0.0230 ±0.0055	0.0169 ±0.0065

* Each value represents mean ± S.D. (n = 3)

Myp (Mean yield pressure), **A (**Intercept at given pressure), **A_0 (**Intercept at zero pressure),**D_A** (Extent of particle rearrangement-Fragmentation property of powder),**D_0** (Die filling and particle

rearrangement at low pressure),$\mathbf{D_B}$ (Particle rearrangement during die filling -Related to particle shape).

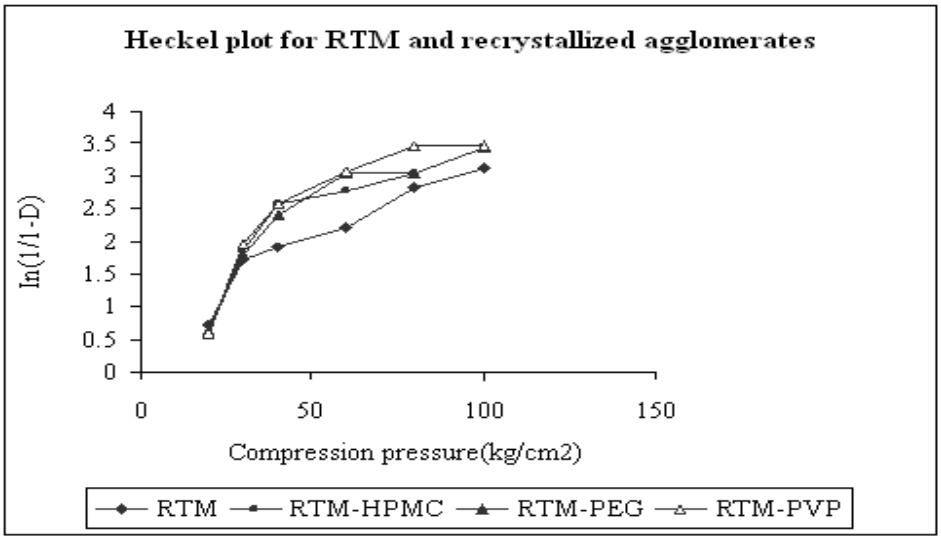

Figure 1. Heckel plot studies of roxithromycin and recrystallized agglomerates

The compacts formed by RTM shows capping and lamination even at lower compression force. This result confirms the weak dependence of the roxithromycin on particle slippage at an early stage of compression however at higher compression pressure capping and lamination occur. The results of the heckel plot study revealed that the recrystallized agglomerates were easily fractured, and the new surface of crystals produced might contribute to promote plastic deformation under compression.

Dissolution study

Figure 2 represents the dissolution of RTM and their recrystallized agglomerates. It is evident that in 30 minutes only 39% cumulative drug release (%CDR) was observed in case of RTM.Where as from the recrystallized agglomerates with hydrophilic polymers more then 60% CDR was observed. The prepared recrystallized recrystallized agglomerates with hydrophilic polymers were showed significantly (**P<0.01) improvement in % CDR at 30 minutes comparative to the raw crystals of RTM. The dissolution profile of recrystallized agglomerates exhibit improvement in dissolution rate comparative to raw crystals of RTM.

The prepared recrystallized agglomerates shows faster dissolution rate compared to RTM. The reason for this faster dissolution could be linked to the adsorption of hydrophilic polymers during recrystallization on the crystal surface and change in crystal habit with crystalline form and also due to better wettability of recrystallized agglomerates. The recrystallized agglomerates with Polymer PVP shows retarded dissolution compared to recrystallized agglomerates with other Polymers like HPMC and PEG. The decreasing dissolution may be attributed to the increase in thickness of the diffusion layer due to the viscosity of the PVP polymer.

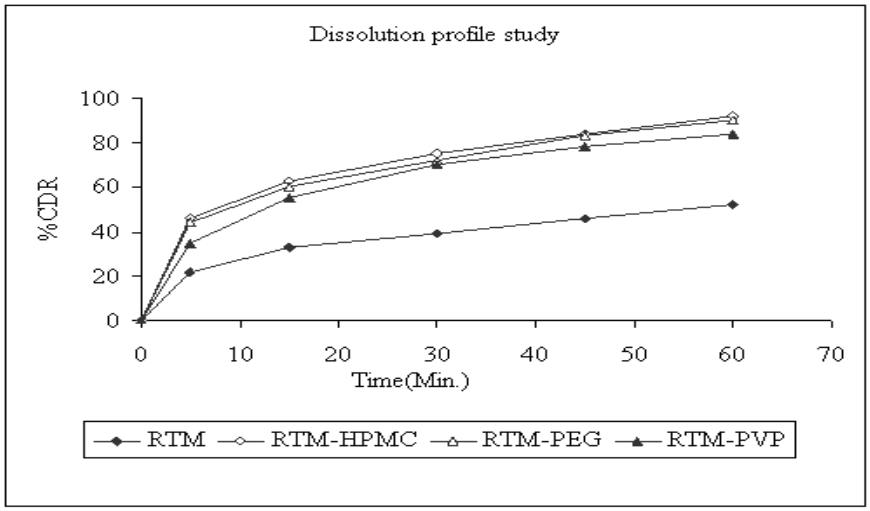

Figure 2. Dissolution profile studies of roxithromycin and recrystallized agglomerates

Fourier transformation-infrared spectroscopy (FTIR) Study

FTIR spectrum (Figure 3) of RTM presented characteristic sharp peaks at 2968 cm−1 (C–H stretching vibration of alkane) and 1726 cm−1 corresponding to carbonyl stretching of the lactone ring containing more than six carbon atoms. These two characteristic peaks were observed in all prepared recrystallized agglomerates with polymers.

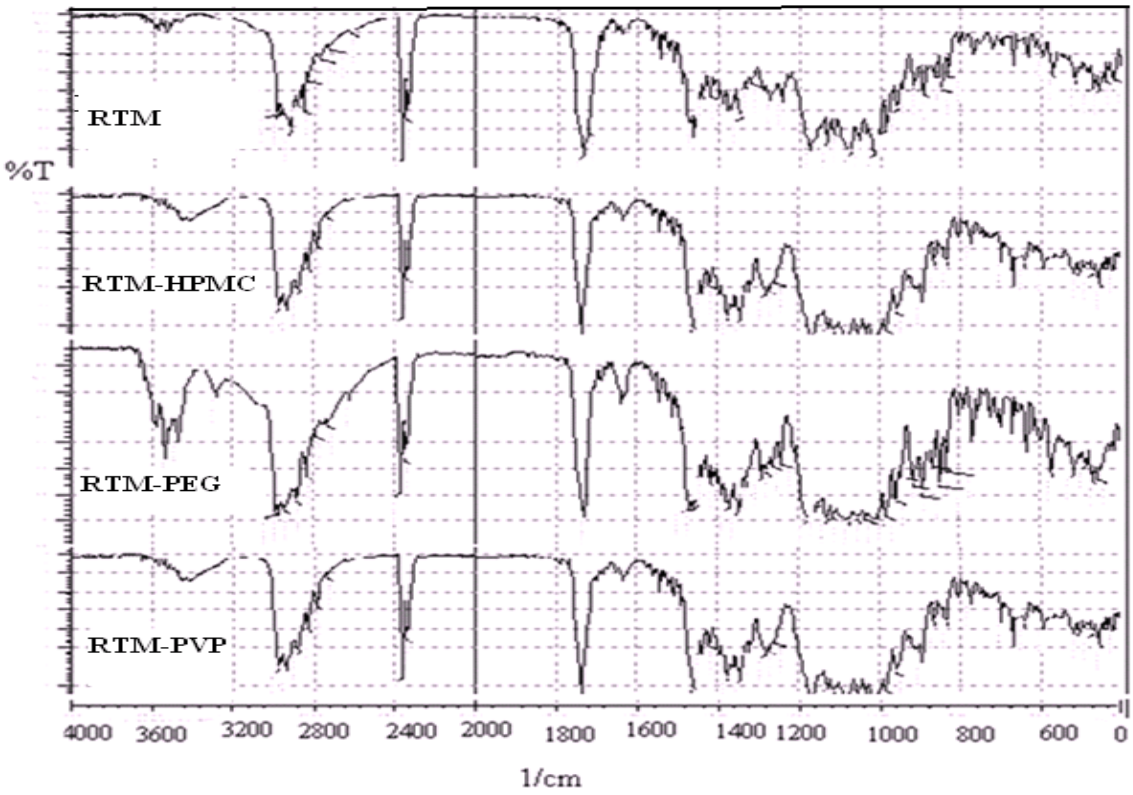

Figure 3. FTIR studies of roxithromycin and recrystallized agglomerates

The closeness between the FT-IR spectra of the roxithromycin and their recrystallized agglomerates suggested that there were no changes in the roxithromycin molecular structure due to the process of recrystallization and agglomeration with different solvents and polymers.

X-ray powder diffractometry (XRD) Study

According to the obtained X-ray power diffraction pattern (Figure 4), RTM shows large number of peaks and having larger peak counts at highest intense peak comparative to prepared recrystallized agglomerates. A few diffuse peaks or decrease in crystallinity were observed in the recrystallized agglomerates with used polymers which may indicate slightly physical interaction of drug with polymers. The decreased drug crystallite size can explain the faster dissolution rate of the recrystallized agglomerated samples.

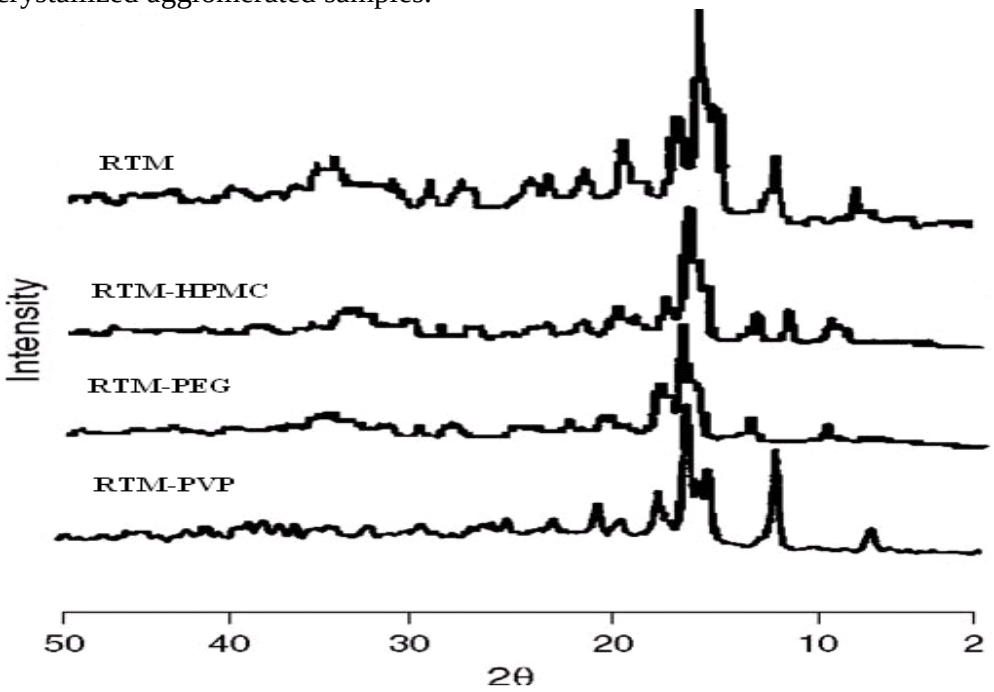

Figure 4. XRPD studies of roxithromycin and recrystallized agglomerates

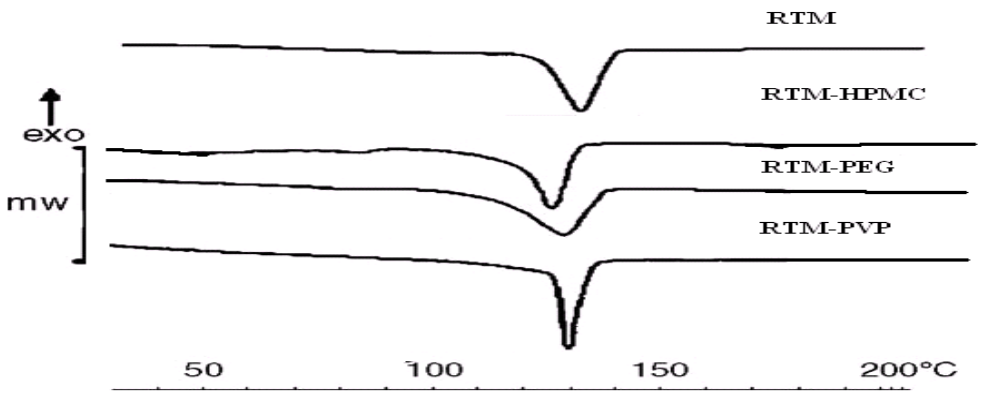

Figure 5. DSC studies of roxithromycin and recrystallized agglomerates

Differential scanning calorimetry (DSC) Study

Figure 5 showed an endothermic peak at 128.86 °C with ΔH—67.43 J g−1 for RTM, which can be attributed to the melting of RTM.The prepared recrystallized agglomerates shows slightly decrease in endothermic peaks indicating conversion of crystalline form of RTM towards the amorphous form.

The XRD study revealed that the prepared recrystallized agglomerates shows diffuse peaks or decrease in crystallinity indicate conversion of crystalline form of RTM towards amorphous also supported by slightly decreased in melting point in DSC peaks.

Scanning Electron Microscopy (SEM)

The surface topography of the RTM and recrystallized agglomerates (Figure 6) was examined using SEM.Accoring to the results obtained the raw crystals of RTM shows stone shaped irregular crystals. The recrystallized agglomerates with HPMC shows spherical shape comparative to the recrystallized agglomerates with PEG and PVP.

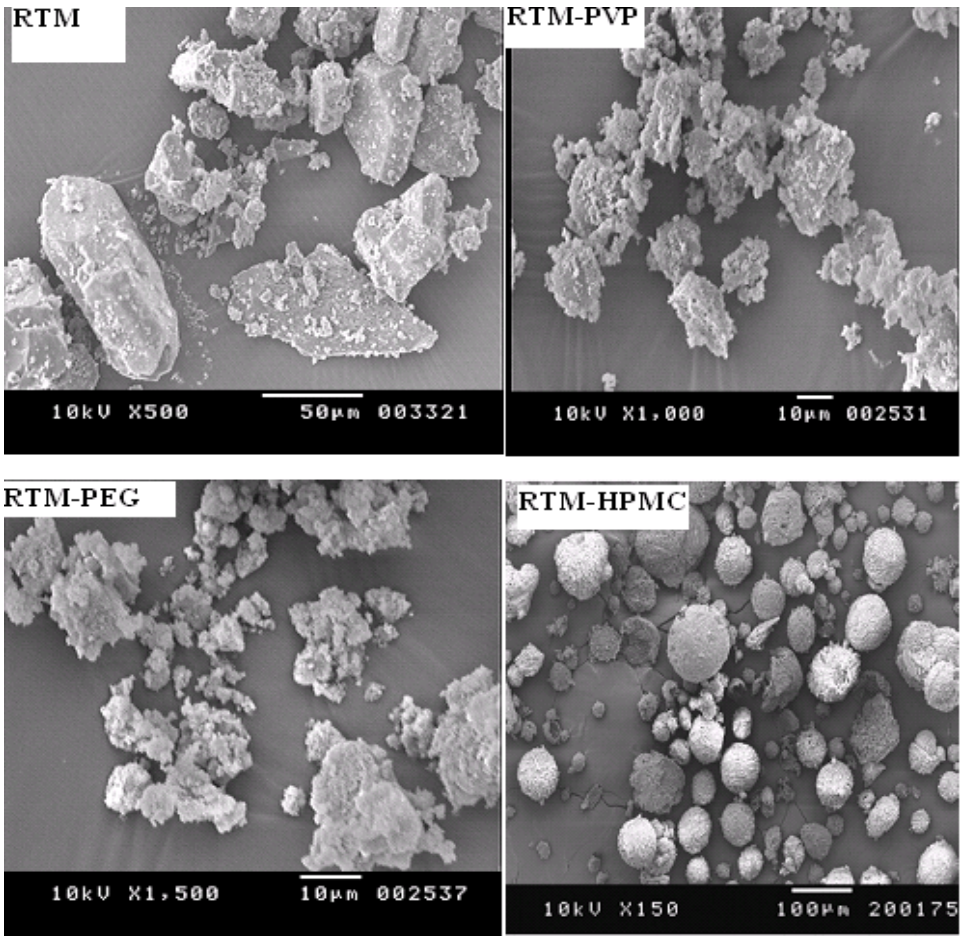

Figure 6. SEM of roxithromycin and recrystallized agglomerates

Thus it is concluded that the used technique is simple, inexpensive enough for scaling up to a commercial level. The used technique reduces time and cost by involving faster operation, less

machinery and fewer personnel with great advances in tabletting technology, especially the introduction of number of directly compressible excipients. By using this technology, physicochemical properties of pharmaceutical crystals dramatically improved for pharmaceutical process i.e. milling, mixing and tabletting because of their excellent flowability, packability and compressibility.

Conclusion

It has been revealed that the solvent change technique with different hydrophilic polymers is an appealing method to improve the solubility, dissolution, flowability, packability, wettability and compression behavior of RTM.The DSC study showed a decrease in the melting enthalpy indicating disorder in the crystalline of RTM. The XRD spectrum shows characteristic decrease in crystallinity. FTIR study reveals that there are no chemical changes in prepared recrystallized agglomerates of roxithromycin. The improvement in flowability contributes to making the filling of the die easier and more precise and thus gives more reproducible results in tablet manufacturing. The prepared recrystallized agglomerates shows increase in tabletability and compactibility properties, helps to obtain a material for direct compression.These properties are probably due to the characteristics of recrystallized agglomerates which consist of an agglomeration of very small recrystallized particles which is favorable for compression.

Acknowledgements

The authors are thankful to Shivaji University Kolhapur Maharashtra, India for providing DSC, FTIR, XRD, SEM facilities. The authors are very much thankful to Dr. S. B. Bhise Principal Govt. College of Pharmacy, Karad, Maharashtra, India for providing laboratory facilities for the research work.

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