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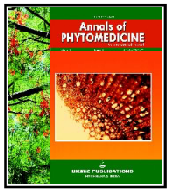

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Solubility enhancement of curcumin, quercetin and rutin by solid dispersion method

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Abstract

Curcumin, quercetin and rutin are pharmaceutical bioactive compounds but their usages are restricted because of low aqueous solubility and wettability which leads to poor dissolution, hence shows low bioavailability. The centre of consideration for this study is to provide solubility enhancement, improved bioavailability and provide a better patient compliance. To improve the hydrophilic and drug delivery characteristics, developed a beta-cyclodextrin and polyvinyl pyrrolidone K30 mediated fixed dose combination drug delivery system *via* solid dispersion technique. Inclusion complex was prepared as a fixed dose combination of these three bioactive phytoconstituent, obtained from natural sources with different polymers. The formations of inclusion complexes were characterized by Fourier transform infrared, drug content and drug dissolution. Saturation solubility studies also indicated that inclusion complex showed markable increased solubility compared toothers. Physical analysis of solid dispersion, when compared to its apparent compounds by FTIR allows for a change in solid state from the pure crystalline phase to the high-amorphous phase. The drug solubility increased in proportion to the increase in the concentration of polymer. The inclusion complex of PHC-β-CD prepared by solvent evaporation method demonstrated higher drug dissolution rates in comparison to solid dispersion prepared by solvent change precipitation method.

1. Introduction

It is well known that the rate of drug dissolution might be the critical restricting step in the bioavailability after oral administration and the therapeutic effect of the drug. In case of low-solubility drugs, the drug absorption from the alimentary tract is generally slow and irregular (Fincher, 1986) and any enhancement of the dissolution would improve its absorption and bioavailability. Many methods are available to improve these characteristics, including salt formation, micritization and addition of solvent or surface-active agents. Solid dispersion (SD) is one of these methods, and involved a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting solvent method (Kaur *et al.*, 2012).

Flavonoids are naturally occurring substances that have a positive result on human health and are present in more than 100 preparations sold in Europe (Peterson and Dwyer, 1998). These molecules show various biological effects, such as capillarity fragility protection, inhibition of lipid peroxidation (Ferrandizand Alcarez, 1991), and anti-inflammatory activity through inhibition of the enzymes involved in arachidonic acid metabolism (Mascolo and Capasso, 1988; Middelton and Kandavasami, 1992).

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In particular, curcumin (Cm), rutin (Rt) and quercetin (Qc) are flavonoids widely distributed in herbal drugs. Cm is very important flavonoids because it has various types of therapeutic application such as anti-inflammation, antimicrobial, antioxidant, antiparasitic and anticancer (Mohan *et al.*, 2012; Yallapu*et al.*, 2010). It is considered safe for human use, even in high doses (Singh *et al.*, 2010; Anand *et al.*, 2007).

In recent years, many Rt derivatives have been employed in clinics to treat venous insufficiency, hemorrhoids, and lymphoedema; Qc has shown antiulcer behavior *in vivo* (Fermin, 1997), and antiproliferative and antimutagenic activity *in vitro* (Kuo, 1996). Unfortunately, these flavonoids are moderately soluble in water and show a slow dissolution rate so, their use in therapy is restricted.

To overcome this problem, we can enhance the drug dissolution rate of Cm, Rt and Qc by inclusion complexation technique and different water-soluble carriers have been employed for preparation of solid dispersion. The most common ones are: poly vinyl pyrrolodone K30(PVPK30) and beta-cyclodextrin (β-CD) (Yallapu *et al.*, 2010; Pranali and Pramod, 2014).

2. Materials and Methods

2.1 Materials

Curcumin, quercetin and rutin were procured from Sissco Research Laboratories Pvt. Ltd. Mumbai, India. All supplementary reagents were used of analytical grade and were provided by local suppliers, Shubh scientific, Lucknow. PVPK30 and β-CD was obtained from

Sigma-Aldrich, USA. All added chemicals used were analytical grade. For this study, various instruments have been used such as FTIR spectrophotometer, UV spectrophotometer (double beam), USP-II dissolution apparatus and vortex mixture.

Method

Preformulation studies characterize the physical, chemical and mechanical properties of novel drug substances, to prepare an advance, stable, safe and fruitful dosage forms.

2.2 Construction of calibration curve

Stock solution (100 µg/ml) of Cm, Rt and Qc were prepared in volumetric flask separately by dissolving 10 mg uniformly in 100 ml of phosphate buffer (pH 6.8) by sonication. The aliquots of 1 ml, 2 ml, 3 ml, 4 ml and 5 ml was pipette out from the prepared standard stock solution into 10 ml volumetric flask and phosphate buffer (pH 6.8) was dispensed to obtained the final concentration of 10, 20, 30, 40 and 50 µg/ml, respectively. The absorbance of each concentration was measured at λ max of 421 nm, 372 nm and 359 nm for Cm, Rt and Qc, respectively using UV Visible spectrophotometer against blank (Seema *et al.*, 2015; Chaudhary *et al.*, 2014; Abualhasan, 2017).

2.3 Preparation of inclusion complex

Polyherbal combination (PHC) inclusion complex was developed to improve the bioavailability by solvent evaporation and solvent change precipitation methods. According to Table 1, different ratios of PHC and polymers were prepared.

Table 1: Formula for trial batches of inclusion complex

S.No.	Method	Polymer	Inclusion complex code	PHC: Polymer ratio
1.	Solvent change precipitation method	PVPK30	SD1	1: 1
2.			SD2	1: 2
3.			SD3	1: 4
4.		β-CD	SD4	1: 1
5			SD5	1: 2
6			SD6	1: 4
7	Solvent evaporation method	PVPK30	SD7	1: 1
8			SD8	1: 2
9			SD9	1: 4
10		β-CD	SD10	1: 1
11			SD11	1: 2
12			SD12	1: 4

2.3.1 Solvent evaporation method

In this method, the weighed amount of drug and polymer were mixed in an organic solvent acetone separately, followed by addition of polymer phase to drug phase. On magnetic stirrer, the solvent mixture was agitated at 40°C and then evaporated in oven at 40°C. The size of obtained coarse particle of solid mass was reduced by trituration method and then sieved through sieve number 44 to get uniform particle size and kept in desiccator for characterization (Pranali and Pramod, 2014).

2.3.2 Solvent change precipitation method

In this method, all three drugs and polymers were dissolved separately in an organic solvent acetone. Then drug solution was added drop wise in the organic solution, containing polymer under overhead stirring, causing precipitation of solubilized drug phase. The precipitated product was then kept in an oven at 40°C till it gets dry. The dried powder was then passed through the sieve no. 44 to get constant particle size and kept in desiccators a for characterization (Mahajan and Bhalkar, 2017).

2.4 Saturation solubility assay

The saturation solubility studies of prepared solid dispersions were performed in 0.1 N HCl, distilled water, and phosphate buffer (PBS) pH 6.8. Pure drug and the inclusion complex with high concentration of polymer were used for this study. Excess of sample was dispersed in the 25 ml of media. A super saturated solution was prepared with continuous stirring for 24 h at required temperature until equilibrium. From same super saturated, solution, 5 ml was filtered through 0.2 µm membrane filters and 1 ml of the filtrate was again diluted and recorded the absorbance at 421 nm, 372 nm and 359 nm, respectively (Mahmoud, 2009).

2.5 Fourier transform infra-red spectroscopy (FTIR)

FTIR study was applied for both pure active ingredient and solid dispersions. The potassium bromide of IR grade was thoroughly mixed with powdered sample and then compressed into clear disc under high pressure using special dies. The disc was placed in IR spectrophotometer using sample holder and spectrum was recorded (Esclusa-Diaz *et al.*, 1996).

2.6 Content of active ingredient

For this purpose, the fine powder of inclusion complex was weighed to get equivalent to 50 mg of each pure drug and transferred into a conical flask which contains 100 ml of distilled water and agitated for 45 min in an ultra sonicator. Solution was filtered and obtained filtrates were analyzed by UV spectrophotometer at 421, 359 and 372 nm for Cm, Qc and Rt, respectively and drug content for all batches were determined. All studies were carried out in triplicates (Indian Pharmacopoeia, 2007).

2.7 *In vitro* dissolution studies

Powder dissolution study was carried out using six stations USP apparatus II (Lab Tree, Haryana) in 900 ml of pH 6.8 at a temperature of 37 ± 0.5°C at 100 rpm. A powdered sample (equivalent 50 mg of each herbal drug) was introduced directly into the dissolution medium. At regular time intervals of 10, 20, 30, 40, 50 and 60 min, suitable amount of sample (10 ml) was withdrawn and same amount replaced by fresh medium to maintain the sink condition. The withdrawn samples were suitable diluted and analysed through UV-Visible spectrophotometer at 421, 359 and 372 nm for Cm, Qc and Rt, respectively. All studies were carried out in triplicates (Debnath *et al.*, 2013).

2.8 Statistical analysis

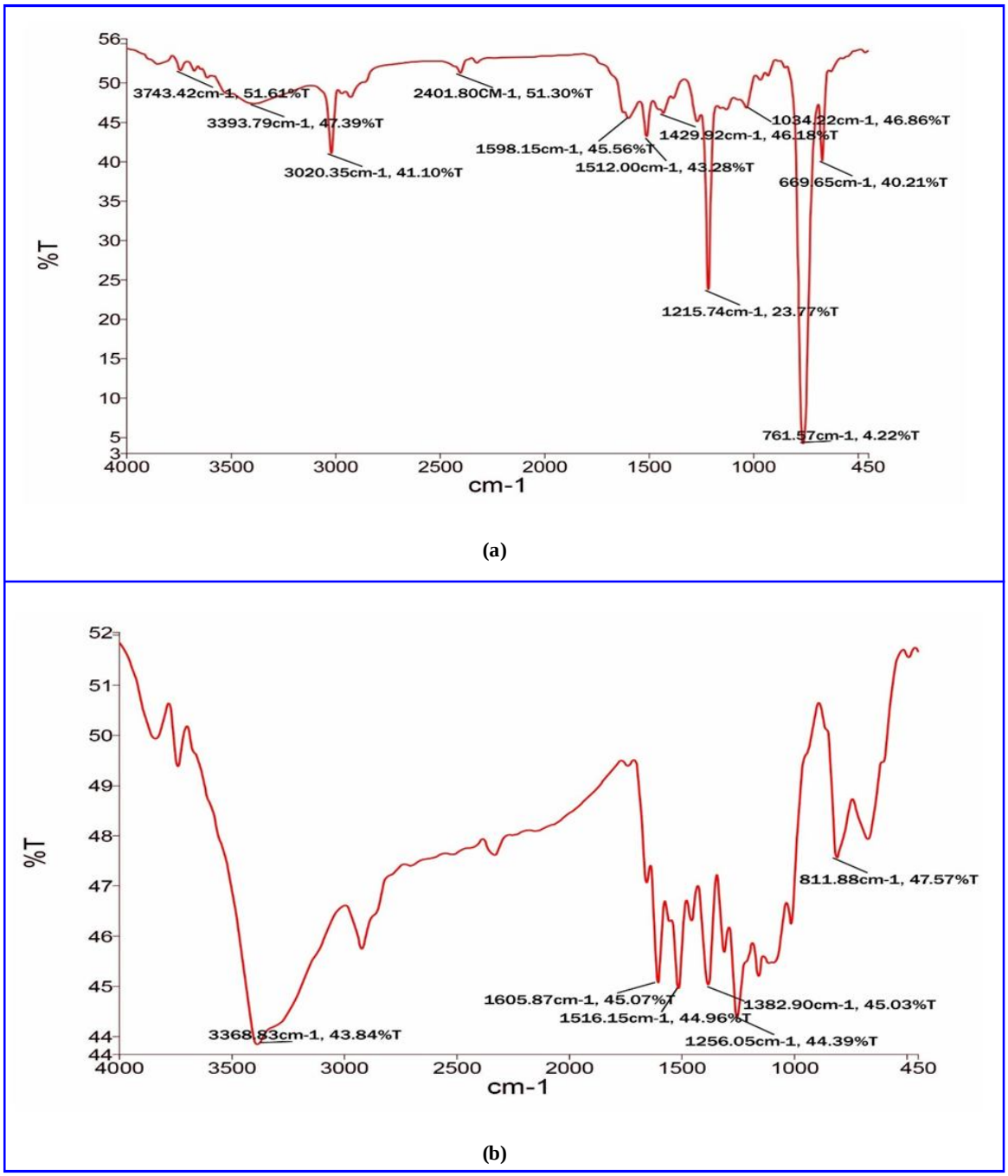
The results were signified as means ± standard deviation (SD). The quantitative statistical analysis was performed by using the

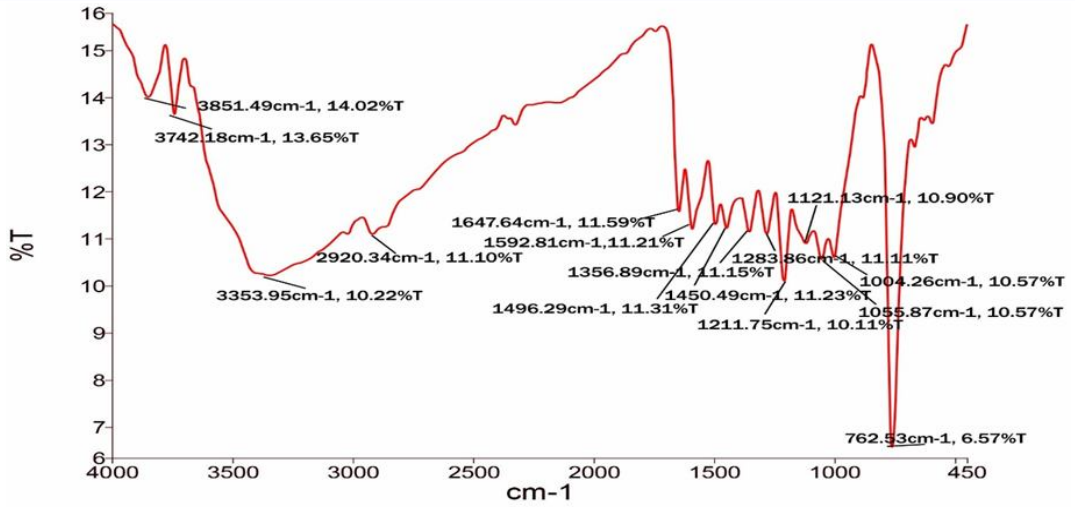
statistical analysis software GraphPad prism 6.0. The differences between the test sample and pure drug were identified by applying analysis of variance (one-way ANOVA), followed by Dunnet test.

3. Results

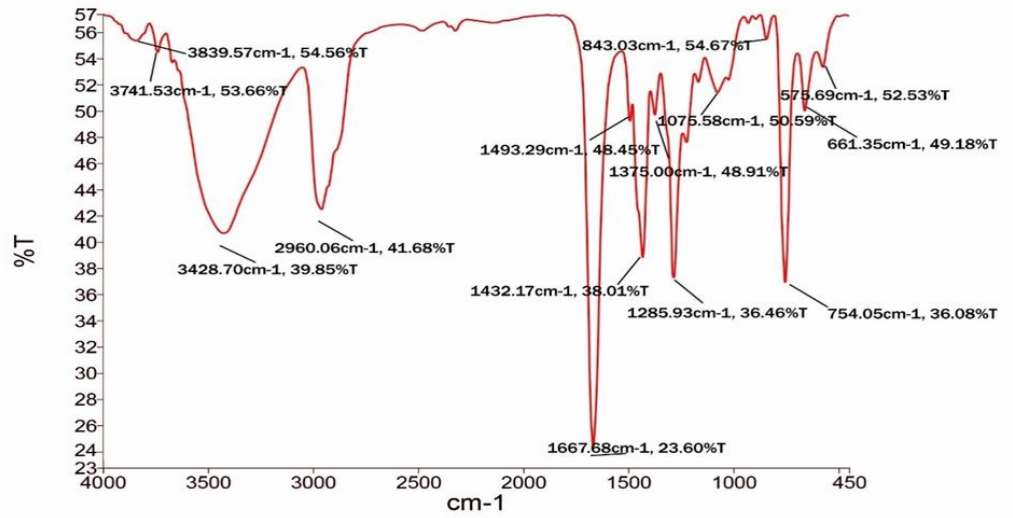
3.1 Fourier transform infra-red spectroscopy (FTIR)

FTIR analyses were supported the interactions between drug and polymer in the solid dispersion systems. The FTIR spectra of pure drug, polymer, physical mixture and solid dispersions are shown in Figure 1. The frequency of vibrations of the bonds attached to the atoms within chemical structure were evaluated by FTIR. The higher frequencies above 3000 cm^{-1} defines the H-bond and moisture content in the molecule. All the individual drugs, excipients, drug mixture and drug excipient mixture have shown peaks above 3000 cm^{-1}, suggesting H-bond stretching and or moisture content. At S 1600 cm^{-1}-C = O stretching was observed in all spectra. However, no remarkable peak has been detected in any mixture of drug excipient and drug-drug mixture. So, it can be concluded that there is no structural interaction between the molecules of drugs as well as drug and excipients and are compatible with each other.

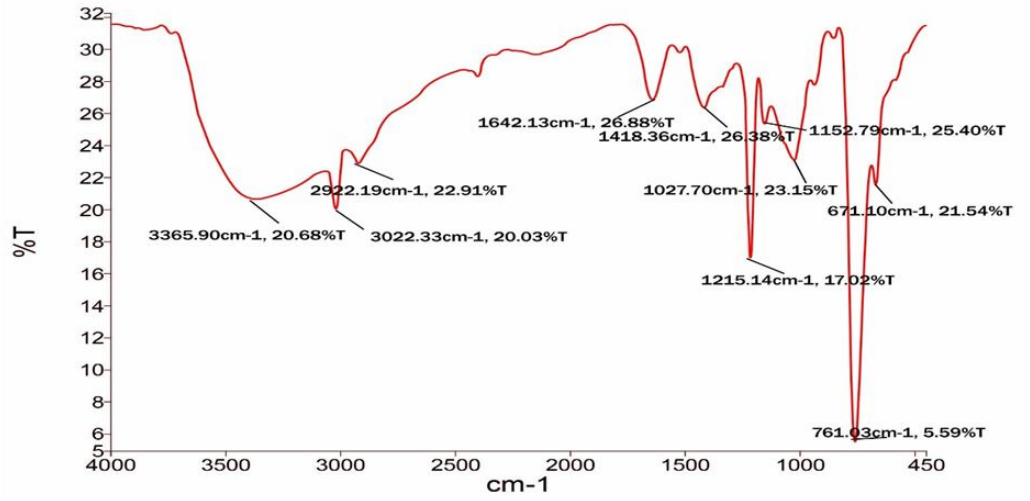



%T
cm-1
3851.49cm-1, 14.02%T
3742.18cm-1, 13.65%T
2920.34cm-1, 11.10%T
3353.95cm-1, 10.22%T
1647.64cm-1, 11.59%T
1592.81cm-1,11.21%T
1356.89cm-1, 11.15%T
1496.29cm-1, 11.31%T
1121.13cm-1, 10.90%T
1283.86cm-1, 11.11%T
1450.49cm-1, 11.23%T
1211.75cm-1, 10.11%T
1004.26cm-1, 10.57%T
1055.87cm-1, 10.57%T
762.53cm-1, 6.57%T

(c)


%T
cm-1
3839.57cm-1, 54.56%T
3741.53cm-1, 53.66%T
2960.06cm-1, 41.68%T
3428.70cm-1, 39.85%T
843.03cm-1, 54.67%T
1493.29cm-1, 48.45%T
1375.00cm-1, 48.91%T
1075.58cm-1, 50.59%T
575.69cm-1, 52.53%T
661.35cm-1, 49.18%T
1432.17cm-1, 38.01%T
1285.93cm-1, 36.46%T
754.05cm-1, 36.08%T
1667.58cm-1, 23.60%T

(d)


%T
cm-1
1642.13cm-1, 26.88%T
1418.36cm-1, 26.38%T
1152.79cm-1, 25.40%T
2922.19cm-1, 22.91%T
3365.90cm-1, 20.68%T
3022.33cm-1, 20.03%T
1027.70cm-1, 23.15%T
671.10cm-1, 21.54%T
1215.14cm-1, 17.02%T
761.03cm-1, 5.59%T

(e)

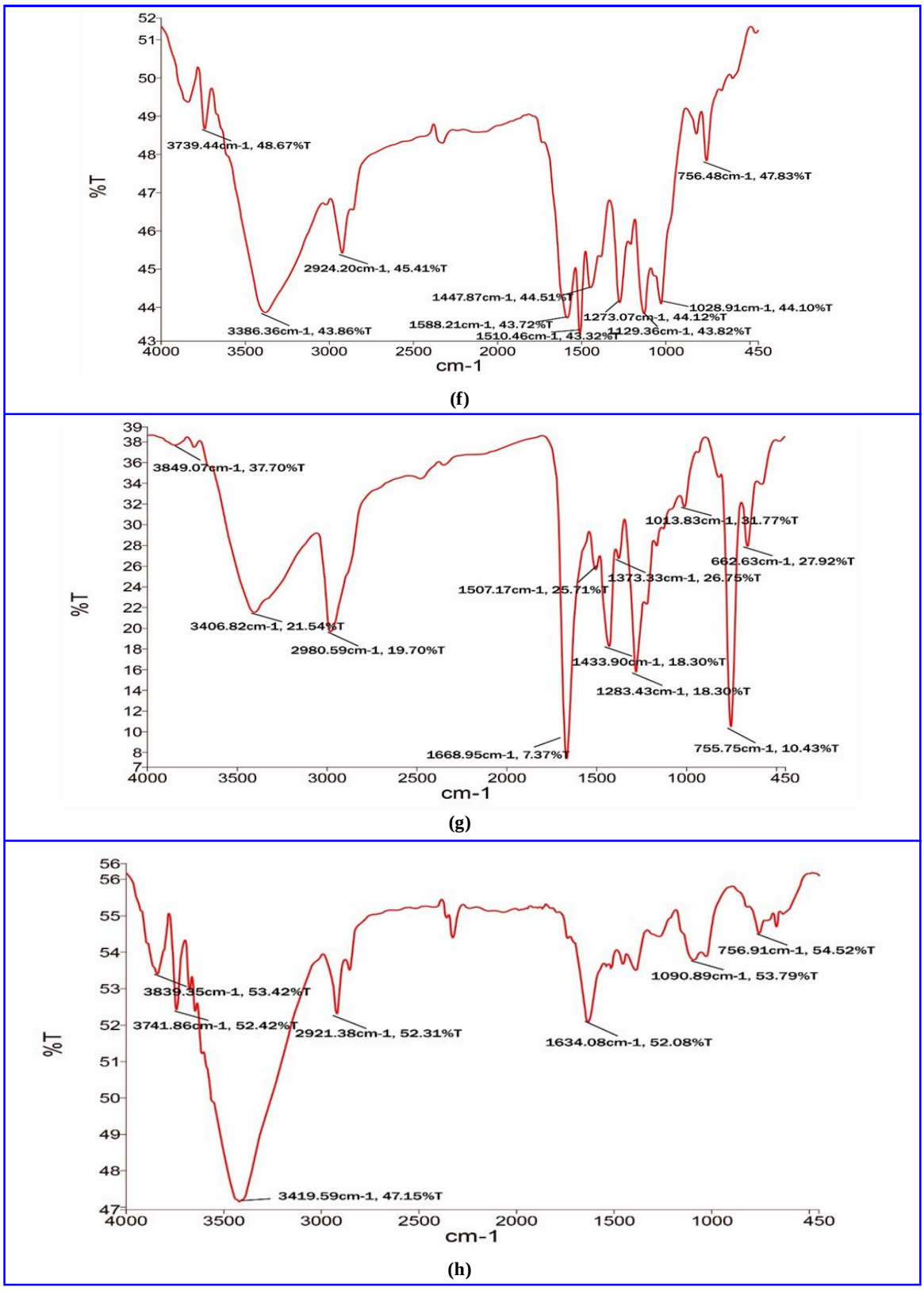


Figure 1: (a) Curcumin, (b) Quercetin, (c) Rutin, (d) ß-cyclodextrin, (e) PVPK30, (f) Simple mixture of PHC with ß-cyclodextrin in 1:1 molar ratio, (g) Simple mixture of PHC with PVPK30 in 1:1 molar ratio, (h) Simple mixture of PHC in 1:1:1 molar.

3.2 Saturation solubility assay

Solubility measurements of pure herbal drug and its solid dispersions are summarized in Figure 2. From the solubility studies of the prepared solid dispersions in different media, it was determined that as the increase in pH of the media increased the solubility. Cm, Qc and Rt showed superior solubility in phosphate buffer pH6.8 when compared with others.

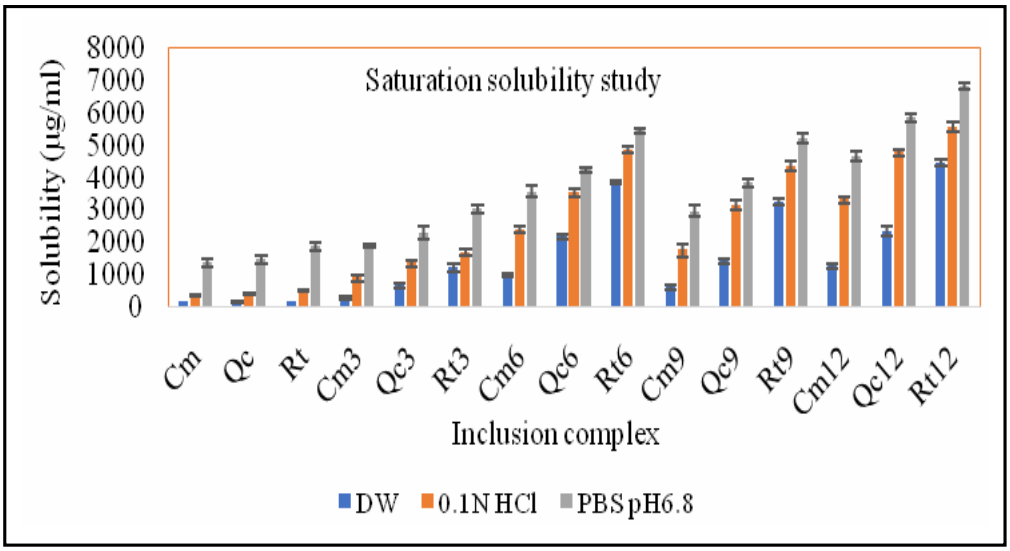
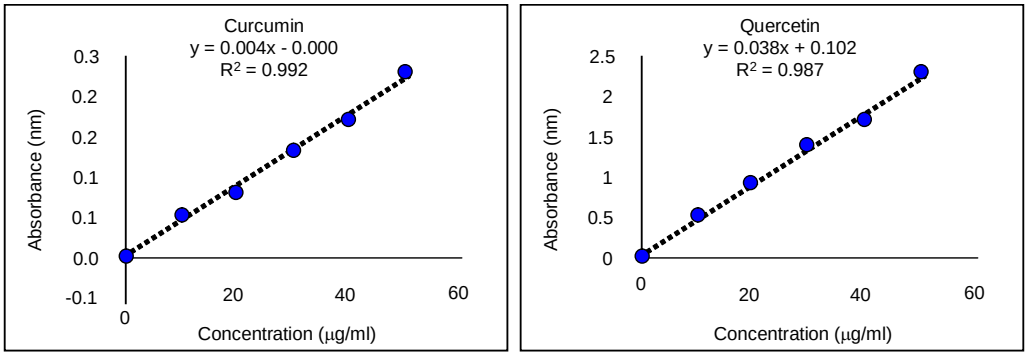


Figure 2: Comparative solubility profile.



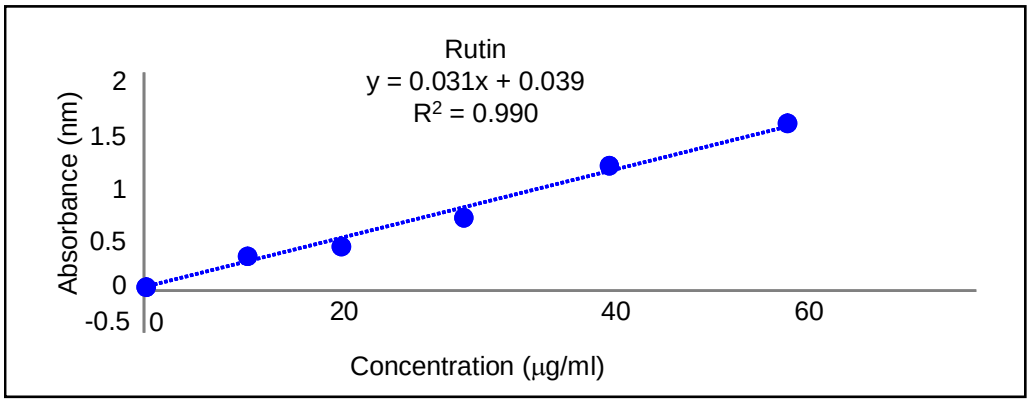


Figure 3: Standard plot of curcumin, quercetin andrutin.

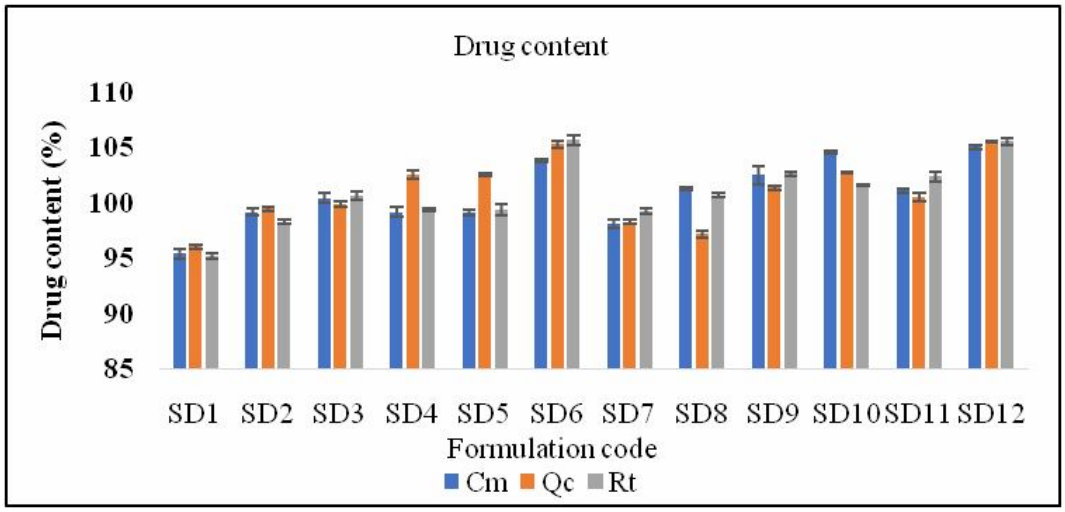
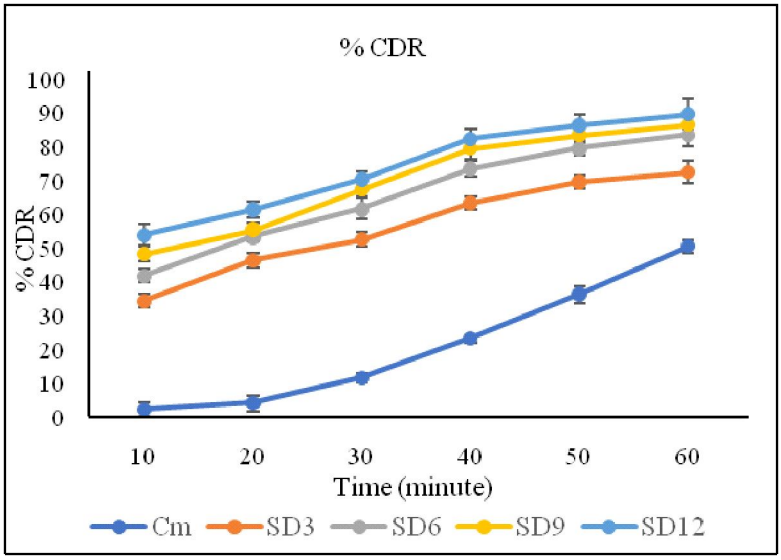
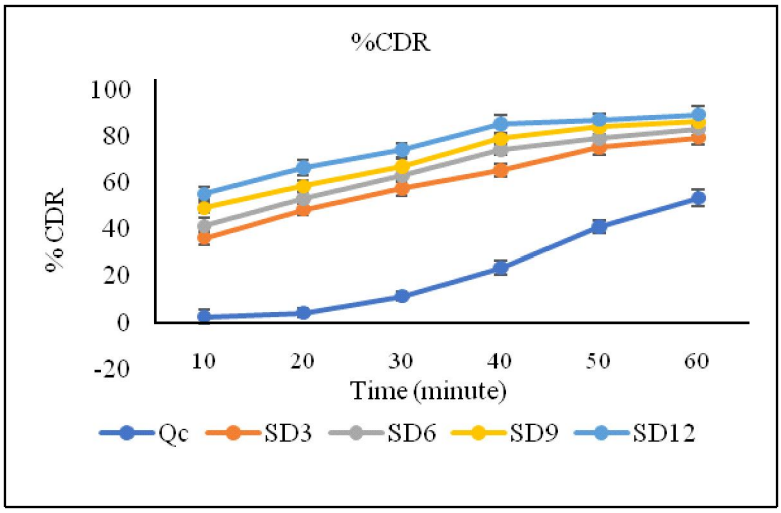


Figure 4: Content of active ingredients.





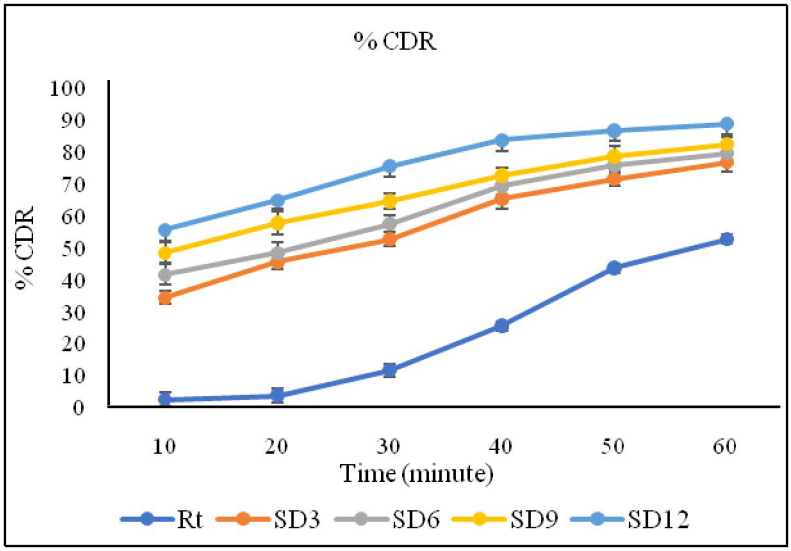


Figure 5: The dissolution profile of curcumin, quercetin and rutin inclusion complex and pure herbal drug.

3.3 Construction of calibration curve

The calibration curves of Cm, Qc and Rt in solution of phosphate buffer pH 6.8. were found to be taken in the range of 10-50 µg/ml. (Figure 3).

3.4 Content of active ingredient

The percentage drugs contents of all the batches were found between 95.41 % to 105.03 %, 95.33% to 105.51%, 95.22% to 105.66% of Cm, Q and Rt, respectively which were within the acceptable limits. All the solid dispersions presented (Figure 4) the availability of high drug content and low standard deviations. It states that the drug is homogeneously dispersed in the powder formulation. Therefore, the method used in this study appears to be reproducible for preparation of solid dispersion.

3.5 *In vitro* dissolution studies

In vitro drug release profile for different batches is shown in Figure 5. During dissolution study, plain Cm, Qc, Rt showed drug release very slow at the end of 60 min. Whereas, drug release of Cm, Qc and Rt in inclusion complex were showed SD3<SD6<SD9<SD12, respectively. The low dissolution rate observed with SD3 and SD6 were prepared by solvent change precipitation and SD9, SD12 were prepared by solvent evaporation method. In case of solvent evaporation method, micron size particles with increased surface area and improved surface wetting property were found to be responsible for solubility and dissolution enhancement. Washing treatment with deionized water leading to removal of water-soluble polymer from the particles surface, might also be one of the reasons for low dissolution rate and solubility in case of SDs prepared by solvent change precipitation technique. SDs prepared by solvent evaporation method, showed maximum drug release and high solubility compared to earlier method, hence it was further characterized. Dispersion of drug into polymer, transition of solid drug from crystalline to amorphous form, reduced particle size and improved surface wetting are the mechanisms responsible for dissolution rate enhancement of solvent evaporated SDs.

4. Discussion

The main focus of the present study was to enhance the solubility of combination of Cm, Qc and Rt with PVPK30 and β-CD to enhance the efficacy and of poorly aqueous soluble drugs. It has been reported previously that supramolecular chemistry of β-CD and PVPK30 offers water soluble inclusion complexes with different drug molecules including antioxidant agents (Yallapu *et al.*, 2010; Borghetti *et al.*, 2009; Quaglia *et al.*, 2009; Corciova *et al.*, 2011). Until now, only a few studies have dealt with increasing the stability and solubility characteristics of Cm, Qc and Rt to improve bioavailability through β-CD and PVPK30 inclusion complexes (Chirio *et al.*, 2009; Mangolim *et al.*, 2014; Xu *et al.*, 2006; Febriyenti *et al.*, 2020; Zheng *et al.*, 2005; Haiyun *et al.*, 2003; Sun *et al.*, 2013). There is no work related to fixed dose combination of these three naturally obtain phytoconstituents, *i.e.*, Cm, Qc, and Rt which explore the synergistic approach regarding the solubility and activity enhancement.

During this process, crystalline form of Cm, Qc and Rt turned out to be highly amorphous in nature. The inclusion complexs of PHC have shown improvement in the aqueous solubility of PHC (Figure 2).

According to previous study, the solubility of curcumin in water is very low in acidic and neutral pH. These flavonoids were soluble in alkali but, rapidly undergoes hydrolytic degradation, which limits its application. The reason for higher solubility of our PHC formulations in aqueous and PBS media is due to better compatibility between drug and polymer in both the techniques. This phenomenon was confirmed by a compatibility study (Figure 1). The higher compatibility of inclusion complexes may provide an increased *in vitro* stability of PHC in aqueous, acidic and in PBS (6.8) medium. All these inclusion complexes had shown high *in vitro* stability at physiological pH conditions (6.8) (Figure 5), whereas Cm did not show significant stability (Borghetti *et al.*, 2009; Nguyen *et al.*, 2013; Kuo, 1996).

The drug content was found to be good and uniform among the different batches of prepared samples. Based on the obtained results

from all of the complex characterisations, complexation efficiencies and solubility assays, PHC-β-CD inclusion complex from solvent evaporation method was selected for subsequent stability.

5. Conclusion

The present study established the influence of the functional conditions of inclusion complex for Cm, Qc and Rt with PVPK30 and β-CD. This study concluded that solvent evaporated inclusion complex showed better solubility and dissolution rate as compared to solvent change precipitated inclusion complexes. This indicated solvent treatmentand inclusion of hydrophilic polymer contributes to enhanced dissolution. The highest improvements in solubility and *in vitro* drug release were observed in SD12, prepared with β-CD by solvent evaporation method in the ratio of 1:4. Inclusion complex prepared by solvent evaporation method are extremely important from a commercial point of view because it improves dissolution profile of poorly soluble drug like Cm, Qc and Rt.

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Conflict of interest

The authors declare no conflict of interest related to this article.

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