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# Formulation and evaluation of atorvastatin tablets by solid dispersion technique

Reza GOUDARZI[1], Mohammad Mehdi MAHBOOBIAN[1*]

1 Department of Pharmaceutics, School of Pharmacy, Hamadan University of Medical Sciences, Hamadan, Iran

**ABSTRACT**

Atorvastatin (ATR) is a low water-soluble drug with a low oral bioavailability. In the present study, the solid dispersion (SD) technique was used to develop a high-soluble formulation of the ATR by the appropriate carrier and then formulated into a tablet. The atorvastatin solid dispersion (ATR-SD) was developed using the polyvinyl-pyrrolidone K30 (PVP-K30) as a carrier in various ratios by the conventional solvent evaporation method. Dissolution studies were done with the select of the optimum drug:polymer ratio. Tablets were prepared by direct compression using various excipients in different ratios to obtain optimum formulation. The highest dissolution rate was obtained for ATR:PVP-K30 ratio of 1:1, which showed a significant increase in dissolution efficiency after 1 hour. Saturated solubility indicated 1.6-fold enhancement for optimum SD formulation compared to the untreated drug. DSC, XRD, and FTIR analysis proved complete amorphization during SD processes. This study provided a new tablet formulation of ATR with enhanced dissolution characteristics by utilizing the SD technique.

**Keywords:** Atorvastatin, solid dispersion, PVP-K30, dissolution rate, direct compression

## INTRODUCTION

Atorvastatin (ATR) as a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor is the most preferred statin to treatment hyperlipidemia by decreasing serum levels of cholesterol, triglyceride, low-density lipoprotein, and increasing level of high-density lipoprotein[1,2]. ATR has solubility and dissolution rate-limited step for absorption. These characteristics lead to low oral bioavailability (12%) and cause to classify in Biopharmaceutical Classification

*Corresponding author: E-mail: m.mahboobian@umsha.ac.ir
ORCIDs:
Reza Goudarzi: 0000-0001-6105-1512
Mohammad Mehdi Mahboobian: 0000-0003-1395-1457
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System (BCS) as class II drug[3]. This characteristic can lead to increasing the daily dose of ATR up to 80 mg to achieve appropriate therapeutic efficiency, which can cause more side effects, especially in the case of polypharmacy[4]. Thus, enhancement in ATR dissolution rate is challenging due to its late release induced by insufficient solubility[5]. Among various approaches used to enhance drug dissolution, solid dispersion (SD) is very popular due to the simple steps of the process and economic efficiency[6]. In SD processes, the drug disperses highly in the hydrophilic carrier. It causes increasing dissolution rate and solubility by different mechanisms such as increase in surface area by decreasing in particle size[7], improvement in drug wettability by direct contact with the hydrophilic carrier and changing in drug crystallinity[8]. SDs can develop by different methods. Among them, solvent evaporation and melting are the most common techniques due to convenience and need of simple facilities[9]. On the other hand, each method has some limitations depending on the physicochemical properties of selected drug and carriers. For instance, the melting method usually happens at high temperatures, which can predispose the drug or carrier to decomposition or in the solvent evaporation method, the drug and carrier dissolve in an organic solvent, and choosing a suitable solvent that could dissolve both the carrier and the drug may be problematic[9,10].

Various grades of polyvinyl-pyrrolidone (PVP) are one of the most hydrophilic carriers to prepare SD formulations[11]. Polyvinyl-pyrrolidone K30 (PVP-K30) with an amorphous state is employed successfully to enhance the solubility of several poor water-soluble drugs such as toltrazuril[12], indomethacin[13], celecoxib[14], gliclazide[15] and meloxicam[16]. Since high glass transition and melting temperature restrict the usage of this polymer for preparing SD by melting method[11]. Therefore, in this study, the solvent evaporation method was selected for preparing atorvastatin solid dispersions (ATR-SDs). Furthermore, different tablet formulations were prepared to evaluate the effect of various excipients on optimum SD formulation and preparation a suitable tablet with satisfactory dissolution efficiency characteristics.

Since tablets are the most common dosage form for oral drug delivery, the direct compression (DC) technique is the shortest and least complex way to fabricate tablets by rightly blending active pharmaceutical ingredient (API) with the suitable excipients and then compressing them into the tablet. DC technique has many advantages comparing wet/dry granulation, including being suitable for thermosensitive, solvent labile, or hydrolysis susceptible drugs and fewer manufacturing steps. On the other hand, considering the importance of flowability and compressibility of excipients in the DC method to certify uni-

form die filling compared to the granulation processes, the selection of excipient types and their amounts in the final formulation is so critical[17,18].

As stated, this study aimed to prepare ATR-SDs by PVP-K30 as the carrier in various drug:carrier ratios. Based on *in vitro* dissolution studies, an optimum ratio was selected for physicochemical characterization and tableting. Tablet formulations contain different excipients and SD powders were designed for DC. Finally, tablets were analyzed for hardness, friability, disintegration time, and dissolution behavior.

## METHODOLOGY

### Materials

Atorvastatin calcium trihydrate was obtained from Sobhan Pharmaceutical Co. (Tehran, Iran). PVP-K30, Talc, and Carboxymethyl cellulose (Croscarmellose sodium) were purchased from Samchun Pure Chemical Co., Ltd (Seoul, Korea). Sodium starch glycolate was provided by Blulux laboratories Reagent, Ltd (India). Magnesium stearate was purchased from Acros Organics (Belgium). Colloidal silicon dioxide (Aerosil) and Microcrystalline cellulose (Avicel PH-102) were purchased from Evonik Degussa (Germany) and Boehringer Mannheim (Germany), respectively. All other chemicals were of pharmaceutical grades.

### Preparation of ATR-SDs

For the preparation of PVP-K30 based SDs by the solvent evaporation method, the calculated amount of drug and carrier (ATR:PVP-K30) in various weight ratios (1:1, 1:3, 1:5, and 1:7) were dissolved in the minimum amount of methanol with constant stirring for 30 min[19]. The obtained solution was kept in the oven (MMM-group, Germany) for 48 h at 45 °C for solvent evaporation and then in a desiccator for 48 h at room temperature to ensure no solvent remained in the mixture. Finally, the residue was sieved through No 100 mesh to get uniformly sized particles.

### Preparation of physical mixture

For investigation of the influence of SD processes apart from the polymer effect, the physical mixture (PM) of the best formulation was prepared by homogenous mixing of drug and carrier, in the selected ratio, which were previously sieved through mesh No 100[20].

### *In vitro* dissolution analysis

The pure drug, SD formulations, and PM, each equivalent to 20 mg ATR, were

subjected to dissolution test for one h in 250 mL phosphate buffer solution (pH=6.8) at 37±0.5◦C[21] for one h and rotating speed of 75 rpm, using a basket dissolution test apparatus (USP dissolution tester apparatus I)[22,23]. At various intervals, 2 mL of the sample was withdrawn and replaced with 2 mL of fresh buffer to keep the sink condition. Then samples were centrifuged (13000 rpm, 10 min), diluted, and spectrophotometrically (Specord 210 plus, Germany) assayed for ATR content at 242 nm[24]. The dissolution efficiency (DE) was deliberate as the area under the dissolution curve up to 60 min and was measured by the trapezoidal method and expressed as a percentage of the area at maximum dissolution.

**Saturated solubility analysis**

Saturated solubility was assayed by adding an excess amount of pure ATR, optimum SD, and relative PM to 1 mL of distilled water in a test tube. Samples were agitated for 72 h at 25±0.5 °C at a rotating speed of 120 rpm using a shaker incubator (Heidolph Unimax 1010, Germany)[25]. Then they were centrifuged, and the supernatant was separated, diluted, and assayed for ATR content by using UV spectrophotometer at 242nm.

**X-ray powder diffraction analysis (XRD)**

The XRD patterns of PVP-K30, ATR, SD, and PM were recorded using an X-ray diffractometer (Malvern PANalytical BV, Netherlands) to investigate the sample crystallinity modification during processes. Samples were subjected to nickel filtered CuKα radiation (K=1.5406 Å), generating at 40 mA and 40 kV and scanned from 2Θ angles of 2° to 70° with a step size of 0.026° [26].

**Differential scanning calorimetry analysis (DSC)**

Thermal analyses of SD, PM, pure ATR, and polymer were performed using DSC200 F3Maia (Germany). Samples were weighed and sealed in aluminum pans and were subjected to heat at a temperature rate of 10°C/min from 32°C to 250°C. Nitrogen gas purge was used throughout the analysis to keep an inert atmosphere. A sealed empty aluminum pan was used as a reference[27].

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

FTIR analysis was done using an FTIR spectrometer (Bruker alpha, tensor 27, Germany). For this purpose, 2 mg of each sample (pure ATR, SD, PM, and PVP-K30) was triturated with 200 mg potassium bromide (KBr) and then compressed into a transparent disk under pressure. The FTIR spectrum of each sample was recorded over a wavenumber range of 4000-400 $cm^{-1}$ and a resolution of 2.0 $cm^{-1}$ [28].

### Preparation of the SD tablets

In order to prepare SD tablets by direct compression method in various formulas, API and excipients were first sieved. Selected SD powder (equivalent to 20 mg ATR) was blended with carboxymethyl cellulose sodium (Croscarmellose sodium), or sodium starch glycolate in 1% and 2% w/w for 10 min as super-disintegrants, and then microcrystalline cellulose (Avicel PH-102) as filler was added to the mixture. Talc or Colloidal silicon dioxide (Aerosil) in various w/w ratios was added as glidant as well. Finally, the mixture was lubricated with magnesium stearate. The tablets were compressed by a single punch tablet press machine (Kavosh Co., Iran). Tablet weight theoretically was 200 mg. The composition of 8 tablet formulations is presented in Table 1.

**Table 1.** Composition of prepared ATR-SD tablets.

| Formulation code | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| ATR-PVP-K30 (mg) | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Sodium starch glycolate (mg) | 2 | 4 | - | - | 2 | - | 4 | - |
| Croscarmellose sodium (mg) | - | - | 2 | 4 | - | 2 | - | 4 |
| Talc (mg) | 2 | 2 | 2 | 2 | - | - | - | - |
| Colloidal silicon dioxide (mg) | - | - | - | - | 2 | 2 | 2 | 2 |
| Magnesium stearate (mg) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Avicel PH 102 (mg) | 154 | 152 | 154 | 152 | 154 | 154 | 152 | 152 |
| Total weight (mg) | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |

### Physical properties of the SD tablets

In order to evaluate SD tablets physical properties, they were analyzed for hardness, friability, and disintegration time.

### Hardness

10 tablets from each formulation were tested using a hardness tester (Erweka, Germany), and breaking strength of each tablet was measured[29].

### Friability

This test was carried out using friability tester (Erweka, Germany). 20 tablets from each formulation were loaded in the drum with speed of 25 rpm for 4 min. The whole weight of tablets before and after test was measured. The friability was calculated as a percentage of weight loss due to abrasion[30].

### Disintegration time

Tablet disintegration test apparatus (Kavosh Co., Iran) was employed to determination of disintegration time of each formulation. The 900 mL of water at a temperature of 37°C±2°C was selected as a disintegration medium. Six tablets at once placed in the apparatus and time taken for all tablets to disintegrate completely was recorded[31].

### Dissolution test

Tablets were also subjected to a dissolution test using USP type II (paddle) dissolution test apparatus with the same condition as previously explained for SD powders[21]. Finally, results were compared with the control tablet (containing untreated ATR by the same tablet formulation as the optimum tablet).

### Statistical analysis

In the present study, data were statistically analyzed by using GraphPad Prism 7 and one-way analysis of variance (ANOVA) followed by Tukey's test was applied. A $P$ value less than 0.05 was served to be statistically significant.

## RESULTS AND DISCUSSION

### *In vitro* dissolution studies

To determine the optimum ratio for further analysis, the dissolution study was first done. Figure 1 illustrates dissolution profiles obtained for intact drug, SDs formulated in various ratios, and corresponding PMs. For all SD formulations containing PVP-K 30 as a hydrophilic carrier, a higher dissolution profile was obtained compared to the intact drug. As shown in Table 2, the maximum dis-

solution efficiency value during 60 min ($DE_{60}$) was obtained for 1-1 drug-carrier ratio, which showed about 32% increases compare to the intact drug, while there was no significant difference between 1-1 and 1-3 ratios (*P* value > 0.05). It was noteworthy that by increasing carrier concentration to 7-fold, $DE_{60}$ was decreased either for SD formulations or PMs. This confirms that the use of PVP-K30 as a water-soluble carrier can highly increase the dissolution rate of the drug. The hydrophilic nature and solubilization capacity of PVP-K30, cause a reduction in interfacial tension between the drug and dissolution medium, which results in drug wettability improvement [14,32]. On the other hand, applying further concentrations of PVP-K30 did not affect as much as lower concentrations (for both SD and PM) due to the generation of a viscous matrix around drug particles, which could hinder drug release by decreasing diffusion coefficient. As shown in Figure 1, in all SD formulations, the dissolution rate was significantly higher than the corresponding PM. Especially for 1-3, 1-5, and 1-7 ratios, the dissolution rates from physical mixtures were approximately like untreated ATR. It confirms that the SD method can remarkably increase the dissolution characteristic of the poorly water-soluble drug through several mechanisms, including the decrease in particle size and accumulation that lead to an increase in surface area and higher drug wettability[7].

**Table 2.** Dissolution efficiency ($DE_{60}$) of various samples (Mean±SD, n=3)

| Samples (ATR:PVP-K30 ratio) | $DE_{60}$ (%) |
|---|---|
| ATR Powder | 49.56±3.61 |
| 1-1 SD | 81.92±1.95 |
| 1-3 SD | 80.89±2.23 |
| 1-5 SD | 73.73±6.8 |
| 1-7 SD | 65.69±3.28 |
| 1-1 PM | 67.27±2.82 |
| 1-3 PM | 55.34±4.49 |
| 1-5 PM | 57.75±0.75 |
| 1-7 PM | 55.88±5.51 |

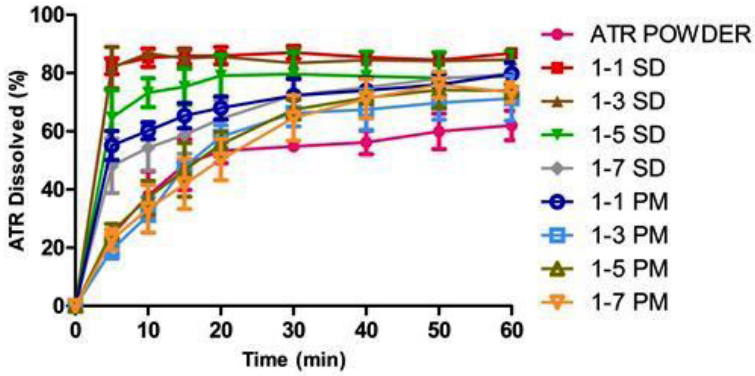


**Figure 1.** Dissolution graph of ATR-SD samples and related PMs (Mean±SD, n=3).

### Saturated solubility studies

Saturated solubility studies were done for formulations that consist of drug-PVP-K30 ratio equal to 1-1, which was the optimum ratio. The saturated solubility of pure ATR in distilled water was 141.02±3.35 µg/mL, which was increased to 171.02±6.34 µg/mL and 229.08±3.61 µg/mL for PM and SD samples, respectively. This solubility enhancement in the presence of a hydrophilic carrier could be associated with intermolecular hydrogen bonding formation between ATR and PVP-K30[33]. As mentioned, PVP-K30 causes a solubilizing effect by decreasing interfacial tension between ATR and release medium[32]. Higher saturated solubility for SD formulation than PM is another evidence for a greater dissolution rate of SD preparation compared to PM.

### X-ray powder diffraction analysis (XRD)

X-ray diffraction patterns of untreated ATR, PVP-K30, optimum SD formulation, and relative PM are presented in Figure 2. PVP-K30 did not show any sharp peak, which indicates its amorphous nature. The XRD pattern of intact ATR showed characteristic peaks at 2Θ values of 9.1, 10.31, 12.23, 16.90, 17.09, 19.49, 21.64, and 23.74 that are related to its crystalline nature[4,27,34]. Completely disappearing of these peaks in SD formulation proves amorphization occurred completely. Whereas in PM diffractogram, ATR characteristic peaks were still presented although with a reduced intensity, which indicated that the crystalline structure of the pure drug still exists with slight amorphization (measured about 7%). Based on the results, high amorphization during SD processes could be the main mechanism for extra elevation in the dissolution rate of the SD formulation compared to the PM[4].

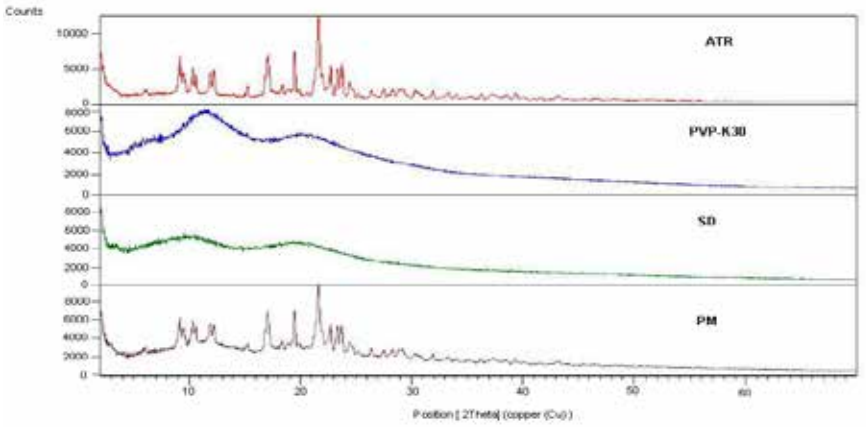


**Figure 2:** XRD patterns of the untreated drug (ATR), PVP-K30, optimum SD and PM.

### Differential scanning calorimetry analysis (DSC)

The results of DSC analysis for SD and PM and components are illustrated in Figure 3. The ATR thermal curve displayed three broad endothermic peaks at 63.63 °C, 99.98 °C, and 125.34 °C related to tree step water loss (due to tri-hydrate form), and the fourth endothermic peak at 157.98 °C is related to the melting point of ATR[24]. PVP-K30 thermogram showed only a broad endothermic peak from 32 °C to 70 °C, corresponding to the loss of water because of the hygroscopic structure of PVP-K30[35]. The absence of any other peaks confirms the total amorphous structure for PVP-K30. No peak was recorded around the ATR melting point in the SD thermogram that confirms entire amorphization. In the corresponding PM thermogram, ATR endothermic peaks were recorded but with extremely low intensity, which proves amorphization occurred not as much as SD sample. In consequence, there was a precise correlation between DSC and XRD studies.

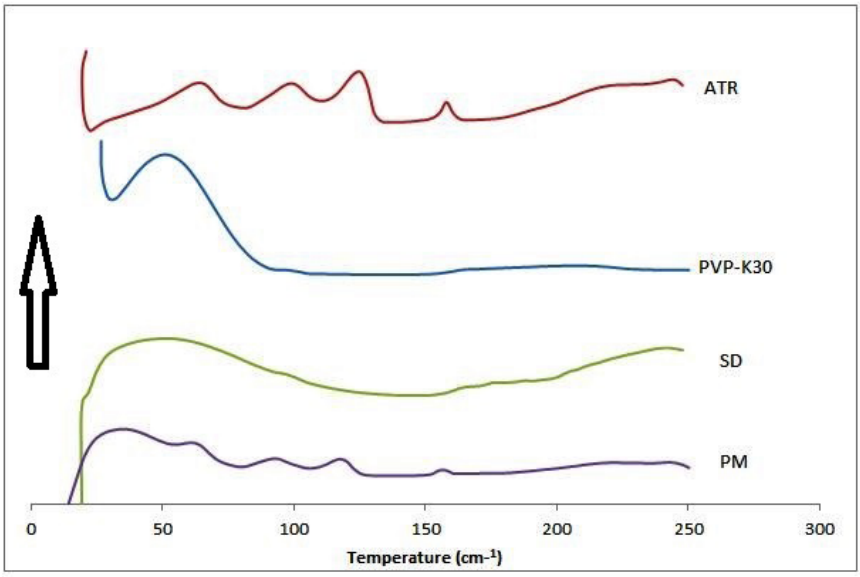


**Figure 3.** DSC thermograms of the untreated drug (ATR), PVP-K30, optimum SD and PM (☐: endothermic peak direction).

### Fourier transform infrared spectroscopy analysis (FTIR)

Figure 4 exhibited the FTIR spectra of ATR, carrier, SD and PM preparation. The PVP-K30 spectrum showed characteristic peaks at 2953.50 $cm^{-1}$ corresponding to the C-H stretching vibration and 1665.99 $cm^{-1}$ related to the C=O band. A broad band at 3467.61 $cm^{-1}$, ascribed to O-H stretching vibration was recorded, due to water presence as DSC finding affirmed[36]. The bulk ATR showed sharp characteristic peaks at 3669.7 $cm^{-1}$ and 3364.5 $cm^{-1}$, corresponding to O-H and N-H stretching, respectively. The C=O asymmetry and symmetry stretching bonds were seen at 1650.5 $cm^{-1}$ and 1579.3 $cm^{-1}$, respectively. The stretching of aromatic C-C bonds were represented at 1552 $cm^{-1}$, 1510.5 $cm^{-1}$, and 1435.8 $cm^{-1}$. The sharp bonds at 1435.86 $cm^{-1}$ related to C-N stretching, and at 1216.51 $cm^{-1}$ linked to C-F stretching vibration. Finally, the C-O stretching bond was recorded at 1159.5 $cm^{-1}$[14]. As it is clear in Figure 4, PM spectra showed the principal characteristic peak of the component with a comparatively sharp appearance, in contrast in the SD sample all characteristic peaks were considerably broadened that attributed to full drug amorphization during SD preparation, confirming DSC and XRD results. Another reason for broader peaks in the SD sample than PM could be related to hydrogen bonding formation between the O-H or N-H group of ATR and the C=O group of PVP-K30 as reported by other researchers for SD development of various drugs with PVP-K30[37,38].

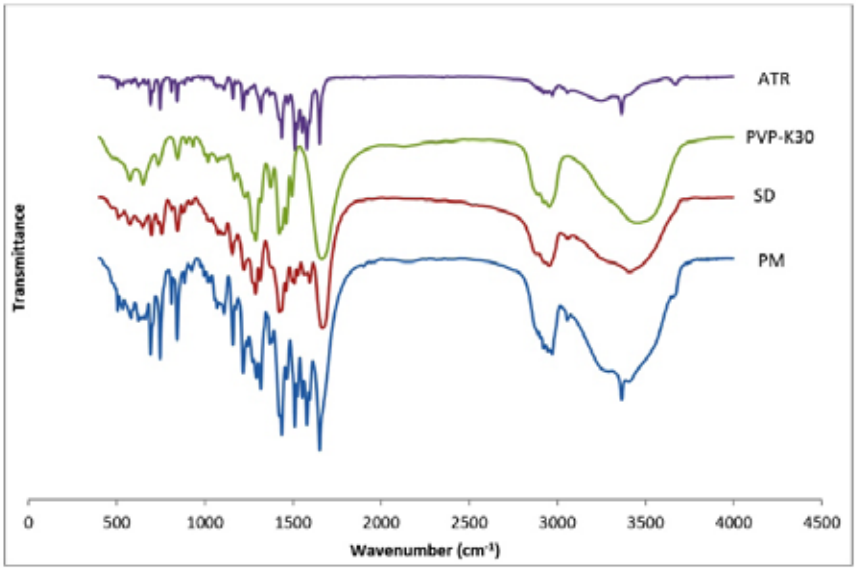


**Figure 4:** FTIR spectra of the untreated drug (ATR), PVP-K30, optimum SD and PM.

## Tableting properties

### Hardness

As shown in Table 3, changes in the type of disintegrants and, also glidants could affect hardness. F3 and F4 formulations in which croscarmellose sodium (CRS) was used as superdisintegrant showed slightly higher hardness than tablets F1 and F2 in which sodium starch glycolate (SSG) was used instead. However, talc was used in all of them as a glidant. But this increase in hardness was contrary in the presence of Aerosil as a glidant, which could be understood by comparing F7 and F8 formulations. In the F7 formulation applying SSG showed significantly higher hardness than applying CRS in the F8 formulation. The same results were obtained for F5 and F6, which are the same in 1% Aerosil. The F5 formulation showed more hardness by use of SSG. By comparison of F2 and F7 formulations, which differed only in the type of glidant, it can be concluded that Aerosil causes tablets to be about two times harder than those prepared by talc. In conclusion, higher hardness values were recorded for formulations containing Aerosil than formulations containing talc. Moreover, in the presence of Aerosil, higher hardness values were measured for those containing SSG.

**Table 3.** Physical properties of prepared tablets (Mean±SD)

| Formulation | Hardness (kp) (n=10) | Friability (%) (n=20) | Disintegration time (min) (n=6) | $DE_{60}$ (%) (n=3) |
|---|---|---|---|---|
| F1 | 4.68±0.42 | 0.72 | < 1 | 88.13±0.17 |
| F2 | 4.92±0.33 | 0.77 | < 1 | 78.88±1.3 |
| F3 | 5.21±0.40 | 0.50 | > 15 | 71.38±1.43 |
| F4 | 5.08±0.23 | 0.58 | > 15 | 61.68±3.08 |
| F5 | 8.67±0.88 | 0.12 | > 30 | - |
| F6 | 7.62±0.9 | 0.04 | > 30 | - |
| F7 | 8.04±0.94 | 0.10 | 15 << 30 | 36.99±.62 |
| F8 | 6.51±0.79 | 0.36 | 15 << 30 | 15.93±3.61 |
| Control | 9.9±0.39 | 0.09 | < 1 | 48.96±0.64 |

Kp: kilopond
min: minute

### Friability

Friability is another factor for evaluating the tablet's physical strength over mechanical stress during the development procedure and transportation[39]. Although the high hardness of the tablet is not always the reason for its low attrition due to the possibility of capping, our funding revealed a logical correlation between hardness and friability (Table 3). However, the friability percentages for all formulations were lower than 0.8%, which met commercial requirements[30].

### Disintegration time

The disintegration time of formulated tablets was analyzed as a distinguished test to guide formulation selection for further analysis. As shown in Table 3, the fastest disintegration time was observed in F1 and F2 by using SSG in 1% w/w and 2% w/w ratios, respectively. There was no significant difference between F1 and F2 formulations. So, control tablet was formulated by the same formulation as F1 (optimum formulation with the lowest percentage of excipients) for better comparison of the effects. It should be noted that the use of talc as a glidant, also helps the tablet to disintegrate easily, even with a lower percentage of superdisintegrant, either SSG or CRS. But in general, SSG showed

better disintegration activity than CRS[40]. It could be concluded that while PVP-K30 (which acts as a binder) is present in the formulation, CRS is not a suitable disintegrant. Also, Aerosil should not use in combination with PVP-K30, due to its moisture adsorbent and thickening agent, which makes the tablet difficult to break up and needs more time to disintegrate[41]. Also, SSG in the concentration of 1% w/w could not disintegrate tablets formulated by Aerosil, while in 2% w/w, it could slowly disintegrate tablets within a long time. The result obtained from the comparison of F3 and F4 formulations was noteworthy. By increasing the CRS ratio, disintegration time did not change significantly, as reported by other researchers to albumin tannate tableting[42]. Finally, maximum disintegration times were shown for F5 and F6 formulations, which took more than 30 minutes to disintegrate, so they were rejected for subjecting to the dissolution test.

**Tablets dissolution properties**

Acquired dissolution profiles for various tablet formulations are represented in Figure 5. The maximum drug dissolution rate was obtained for F1 formulation that showed 90% drug dissolved within 15 min. The Control Tablet that contained untreated ATR with the exact formulation of F1 showed approximately half the dissolution rate of the F1 formulation. It proves that drug dispersion in a suitable carrier (SD preparation) could become a promising strategy in new formulation development that shows a higher dissolution rate. By comparison of F1 against F2 and F3 against F4, it can assume that when the tablet disintegrates well in a lower percentage of disintegrant, increasing in concentration of disintegrant results in a lower dissolution rate and haven't any benefit on disintegration time. At higher concentrations, a thick barrier rises at the release medium around the tablet due to the high viscosity of the superdisintegrant, which could hinder the disintegration or dissolution of tablet components[41]. As shown in Table 3, the $DE_{60}$ values obtained for F7 and F8 formulations weren't desirable due to their long disintegration time (more than 20 min). It can conclude that Aerosil is not a suitable glidant for the formulation containing PVP-K30, which acts as a strong binder, because of the high rigidity created for the formulation that could hinder tablet disintegration and drug dissolution.

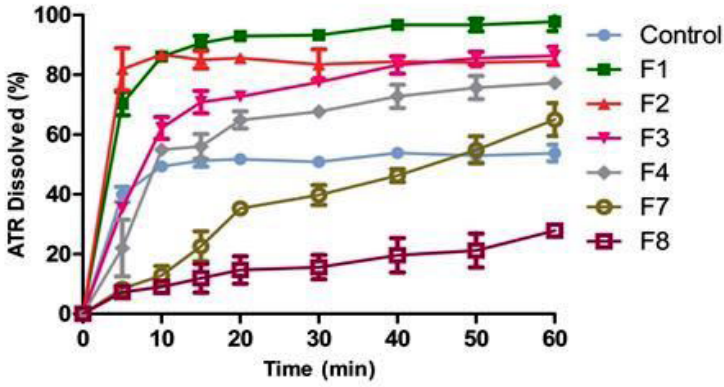


**Figure 5.** Dissolution graph of ATR tablets (Mean±SD, n=3).

## CONCLUSIONS

The present study exhibited that the SD technique, developed by solvent evaporation method and PVP-K30 as a carrier, could improve the dissolution characteristic of ATR effectively, as a poor-soluble drug. It was found that using PVP-K30 in the least ratio, which is in equal proportion to the ATR, causes the maximum increase in the dissolution rate (up to 80%) in the first 10 min. It seems that in addition to the selection of the appropriate polymer, choosing the correct concentration has a great effect on increasing the dissolution rate over a period of time. Also, more than 60% elevation of ATR saturated solubility was obtained by using this method of preparation. The findings of the solid-state characterizations revealed that the total amorphization of ATR-PVP-K30 SD could be the key factor for this dissolution rate enhancement. Furthermore, to formulate an efficient tablet from optimum ATR-PVP-K30 SD (1:1 ratio), SSG at 1% w/w as a disintegrant, talc at 1% w/w for lubrication, and magnesium stearate at 1% w/w besides Avicel PH 102 were found to be suitable components to formulate SD based tablets of ATR.

## STATEMENT OF ETHICS

None.

## CONFLICT OF INTEREST

The authors report no conflicts of interests.

## AUTHOR CONTRIBUTIONS

Reza Goudarzi; Investigation, Writing - Original Draf. Mohammad Mehdi Mahboobian; Conceptualization, Supervision.

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