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SOLUBILITY AND DISSOLUTION ENHANCEMENT OF A BCS CLASS II DRUG BY CO-GRINDING WITH SUPERDISINTEGRANTS

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ABSTRACT

Majority of drugs administered by oral route exhibit low bioavailability because of their limited water solubility. Atorvastatin calcium (ATR)-a potent antihyperlipidemic drug- is a poorly soluble BCS class II drug. Present investigation was aimed at solubility and dissolution enhancement of ATR by co-grinding it with superdisintegrants. Atorvastatin calcium was milled with crospovidone (CP), croscarmellose sodium (CCS) and sodium starch glycolate (SSG) in different ratios using a ball mill. Prepared co-ground mixtures were evaluated by saturation solubility studies, Fourier Transform Infrared (FTIR), X-Ray Diffraction (XRD), Differential Scanning Calorimetry (DSC), and Scanning Electron Microscopy (SEM). Infrared spectrum ruled out any chemical interactions between drug and superdisintegrant. DSC and XRD studies proved that the co-grinding has caused reduction in drug's crystalline characteristics. Also, SEM study indicated micronisation and intimate mixing of drug particles with superdisintegrant. Solubility studies revealed significant solubility enhancement in all co-ground mixtures than that of pure drug and drug milled alone. Tablets were formulated from all co-ground mixtures and evaluated. All the tablet formulation containing co-ground mixture exhibited improved *in-vitro* dissolution. Co-ground mixture with superdisintegrant CCS showed highest solubility and dissolution enhancement in the ratio 1:3. The optimized tablet formulation (F6) displayed better dissolution profile than a marketed formulation. Thus, solubility and dissolution of ATR was successfully enhanced by co-grinding it with superdisintegrants. Co-grinding with superdisintegrant could be concluded as a simple, novel and effective tool for solubility and dissolution enhancement of BCS class II drugs.

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INTRODUCTION

Oral route of drug administration has been a very convenient and widely accepted for most of the therapeutic agents [1]. Many times, it is the poor solubility and drug dissolution that leads to low bioavailability of orally administered drugs than limited permeation through the epithelial lining of the gastrointestinal (GI) tract. Hence, in case of oral administration, the solubility and dissolution characteristics of a drug along with permeability are key determinants of its bioavailability [2]. The dissolution act as the rate determining step to elicit therapeutic effect when a poorly water soluble drug is orally administered [3].

The dissolution profile of BCS class II drugs is needed to be clearly defined and should be reproducible also. It should exhibit a high absorption number (A_n) and a low dissolution number (D_n). The drugs belonging to this class have a variable dissolution pattern mainly because of the formulation and *in vivo* variables affecting the process of absorption [4].

There are a lot of approaches for the improvement of solubility and dissolution rate of poorly soluble drugs. Modifications of the drug substance and the development of particular formulations are the ways utilized for this purpose. Modifications in drug's physical properties include increasing the surface area, solubility and wettability of drug particles. Micronisation or conversion to an amorphous state is the objectives of such physical modifications to affect solubility and dissolution. Various milling techniques have been utilized for particle size reduction and variety of milling equipments are available [5]. But milling poorly soluble drugs alone lead to problems of agglomeration due to hydrophobicity which in turn reduce area available for dissolution. This is highly undesired when developing capsule or tablet formulations [2].

Co-grinding process involve dry milling of an active substance and a hydrophilic or hydrophobic carrier in powder form in a mill [6]. Co-grinding is done under either dry [2, 3, 5, 6] or wet [7] conditions. Different drugs and hydrophilic excipients are reported for solubility and dissolution enhancement by co-grinding [2, 3, 5-7, 9-13].

Atorvastatin calcium (ATR) [R-(R', R')]-2-(4-fluorophenyl)-beta,delta- dihydroxy- 5- (1- methylethyl)-3-phenyl-4 [(phenylamino) carbonyl]- 1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate, is a potent antihyperlipidemic drug of class HMG-CoA reductase inhibitor but is very slightly soluble in water and its oral bioavailability is 14% [8]. Therefore, in order to obtain sufficient bioavailability, water solubility and dissolution of ATR in oral formulation is needed to be enhanced significantly.

Present study was aimed at solubility and dissolution enhancement of ATR by co-grinding it with commonly used superdisintegrants like crospovidone (CP), croscarmellose sodium (CCS) and sodium starch glycolate (SSG), with different drug to superdisintegrant ratios, in a ball mill. Also, the purpose was to understand underlying mechanisms and effect of above mentioned superdisintegrants on solubility and dissolution enhancement with the help of Fourier Transform Infrared (FTIR) spectral analysis, Differential Scanning Calorimetry (DSC), X-ray Diffractometry (XRD) and Scanning Electron Microscopy (SEM).

MATERIALS AND METHODS

Materials

ATR was obtained as a gift sample from Glenmark pharmaceuticals Ltd., Mumbai, India. Crospovidone, Croscarmellose sodium and Sodium starch glycolate were purchased from Research lab ltd., Islampur, India. All other chemicals and reagents used were of analytical grade.

Methods

Preparation of co-ground and physical mixtures

ATR was milled with each superdisintegrant in ratios of 1:1, 1:2 and 1:3 for 6 hours using a laboratory ball mill (Roxel). The 6 hours consisted six cycles each of 1 hour. After completion of each cycle, the adhered powder was removed from the wall of the vessel with spatula for proper mixing. Similarly, ATR was milled alone. The physical mixtures with same ratios were prepared by simply mixing the drug and superdisintegrant in the mortar and pestle for 10 mins. All co-ground and physical mixtures were stored in air tight plastic bags with proper labeling.

Characterization of prepared co-ground mixtures

Saturation solubility studies

Saturation solubility studies of pure ATR, milled ATR and all co-ground mixtures were performed in distilled water according to method reported by Higuchi and Connors. Excess of pure ATR was added to 25 ml distilled water taken in volumetric flasks. The flasks were shaken for 48 hrs using water bath shaker (Samarth, Mumbai, India) at 25°C. After the complete equilibration, the supernatant solutions were collected carefully and filtered using 0.45 µm membrane filters. The concentration of ATR in filtered solution was determined using UV visible spectrophotometer [14]. The procedure was carried out in triplicate for each mixture. Optimized co-ground mixture was selected from saturation solubility data.

Fourier Transform Infrared (FTIR) analysis

FTIR spectra of pure ATR, milled ATR, superdisintegrant, physical mixture and optimized co-ground mixture were recorded by using Fourier Transform Infrared Spectrophotometer (Model ALPHA- E, Bruker). Scanning was done from 400 to 4000 cm⁻¹.

X-Ray Diffractometry (XRD)

X-ray diffraction patterns of pure ATR, milled ATR, superdisintegrant, physical mixture and optimized co-ground mixture were recorded using X-ray Diffractometer (PW 1729, Philips, The Netherlands) with a copper target, voltage 30 kV, current 30 mA over 2θ range of 10-70°.

Differential Scanning Calorimetry (DSC)

Thermograms of pure ATR, milled ATR, superdisintegrant, physical mixture and optimized co-ground mixture were recorded using instrument equipped with an intracooler (Mettler- Toledo, Switzerland). About 5 mg of samples were sealed in aluminum pans and heated at the rate of 10°C/min from 30°C to 200°C under nitrogen atmosphere of flow rate 40 ml/min.

Scanning Electron Microscopy (SEM)

Electron micrographs of pure ATR, milled ATR, physical mixture and optimized co-ground mixture were obtained using a scanning electron microscope (JSM 5600 LV Joel, Japan) operating at 15 kV. The specimens were mounted on a metal stub with double-sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation.

Formulation of tablets

Composition of all formulation batches is given in Table I. Pure drug or milled drug or Co-ground powder for each formulation and spray dried lactose were mixed for 15 minutes in porcelain mortar, passed through 60 # sieve. Talc and magnesium stearate were added. Prepared powder admixtures were subjected to flowability evaluation studies like determination of angle of repose, Carr's index and Housner's ratio [15]. The powder admixtures equivalent to 10 mg of ATR were directly compressed by using 6 mm round flat-faced punch of KBR press (SL-89, Spectra Lab) under constant force.

Table I: Formulation of co-ground ATR tablets.

| Ingredients | Pure drug | Milled drug | ATR+SSG | | | ATR+CCS | | | ATR+CP | | |
|---------------------|-----------|-------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| | | | 1:1 | 1:2 | 1:3 | 1:1 | 1:2 | 1:3 | 1:1 | 1:2 | 1:3 |
| | | | F ₁ | F ₂ | F ₃ | F ₄ | F ₅ | F ₆ | F ₇ | F ₈ | F ₉ |
| Pure drug | 10 | - | - | - | - | - | - | - | - | - | - |
| Milled drug | - | 10 | - | - | - | - | - | - | - | - | - |
| CCS | 20 | 20 | - | - | - | - | - | - | - | - | - |
| Co-ground mixture* | - | - | 20 | 30 | 40 | 20 | 30 | 40 | 20 | 30 | 40 |
| Spray dried lactose | 92 | 92 | 102 | 92 | 82 | 102 | 92 | 82 | 102 | 92 | 82 |
| Magnesium stearate | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Total Weight | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 |

All quantities are in mg. * equivalent to 10 mg of ATR.

Evaluation of prepared tablets

The formulated tablets were evaluated by performing various quality control tests like uniformity of weight, hardness, friability, uniformity of content, disintegration test and *in vitro* dissolution test as per standard procedures given in Indian Pharmacopoeia (IP) [16, 17]. Optimized formulation was compared with available marketed formulation for *in vitro* drug release.

Statistical analysis

The results of dissolution test were statistically analyzed by one-way ANOVA followed with Tukey's multiple comparison test. Results were quoted as significant where $P < 0.05$.

RESULTS AND DISCUSSION

FTIR analysis

The spectra of different samples analysed are shown in figure I. Pure ATR displayed bands of C=O carboxylic group at 1650 cm^{-1} , NH group at 3529 cm^{-1} , C-O- ester at 1267 cm^{-1} and C-N stretching at 1311 cm^{-1} . They were also present in the spectra of physical mixture and co-ground mixture at similar positions and were not shifted. Thus, addition of drug into superdisintegrant did not cause any interactions involving its functional groups. Hence FTIR study ruled out any interaction between drug and superdisintegrant during co-grinding.

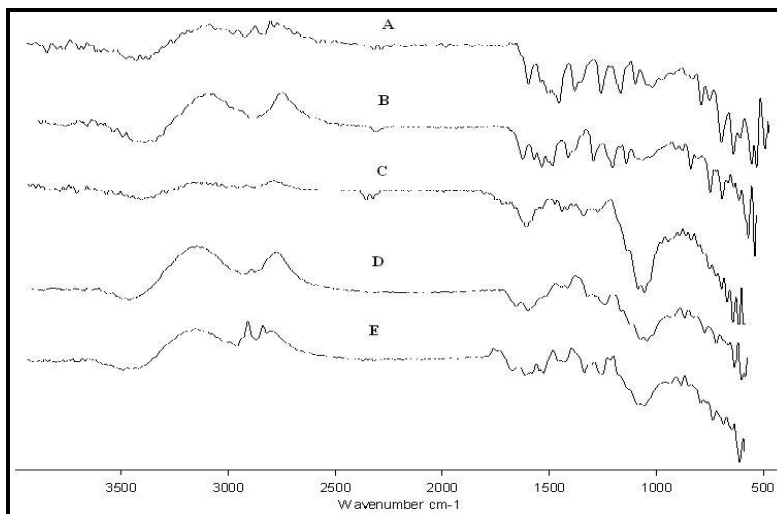


Figure 1: Overlain FTIR spectra showing A-Pure Atorvastatine calcium(ATR), B-Milled Atorvastatine calcium(ATR), C-Croscarmellose sodium(CCS), D-Physical mixture E-Optimized co-ground mixture.

X-Ray Diffraction (XRD)

All the study results are given in figure II. The diffractogram of pure drug demonstrated numerous sharp peaks at 2θ of 12.4, 13.2, 13.4, 18.4 and 18.8⁰ that pointed the drug was crystalline in nature. In case of milled ATR it was observed that the crystallinity of the drug was slightly reduced. Milling the drug alone did not bring significant reduction in crystallinity. XRD pattern of CCS showed absence of sharp peaks, indicating its amorphous nature. In the diffractogram of physical mixture all the principal peaks of drug were present. Co-ground mixture displayed considerable reduction in crystallinity as most of the principal sharp peaks were absent.

Differential Scanning Calorimetry (DSC)

DSC thermograms are shown in figure III. Pure drug exhibited an endothermic peak corresponding to its melting point at 159.69°C. Milled drug sample also showed peak at similar position indicating slight decrease in crystallinity. Superdisintegrant CCS showed a broad endothermic peak in the range of 80-110°C. In physical mixture, endothermic melting peak was present but showed decrease in the intensity. The absence of melting endothermic peak in case of co-ground mixture indicated towards amorphous characteristics of mixture. The crystalline to amorphous change in case of co-ground mixture was previously evident from XRD study. Therefore, DSC study confirms significant reduction in drug's crystallinity after co-grinding with superdisintegrant and its conversion to amorphous form.

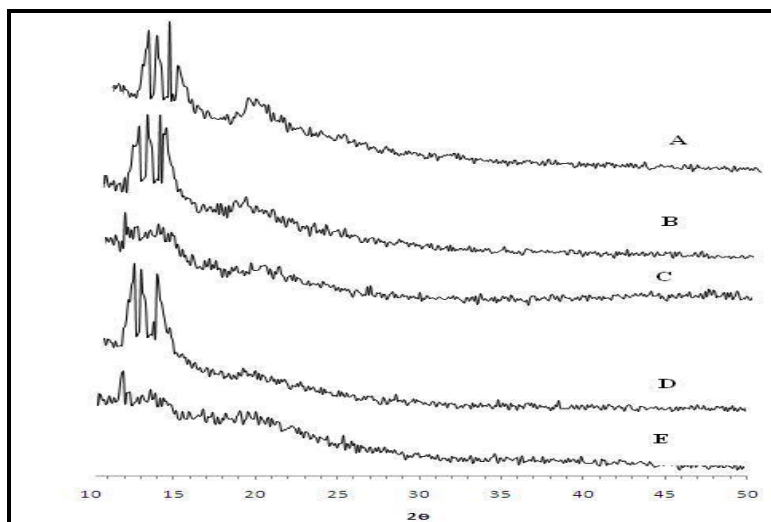


Figure 2: Diffractograms showing A: pure Atorvastatine calcium (ATR), B: milled Atorvastatine calcium (ATR), C: Croscarmellose sodium (CCS), D: physical mixture and E: Optimized co-ground mixture.

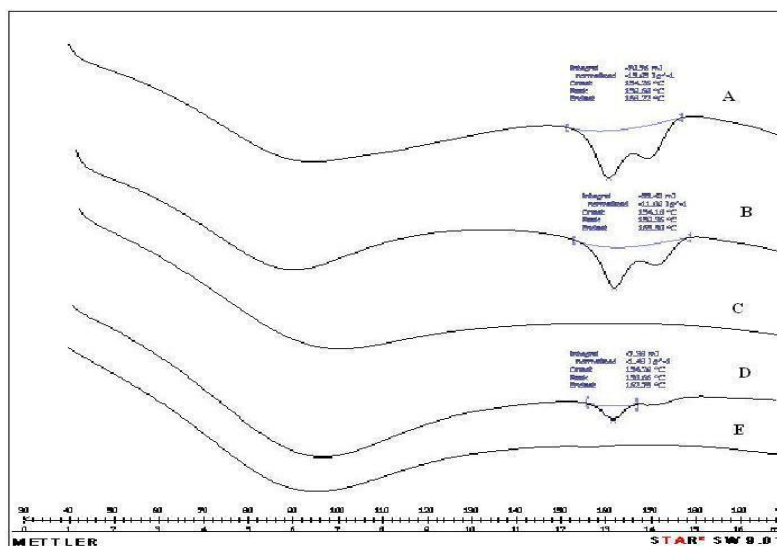


Figure 3: Thermograms showing A: pure Atorvastatine calcium (ATR), B: milled Atorvastatine calcium (ATR), C: Croscarmellose sodium (CCS), D: physical mixture and E: Optimized co-ground mixture.

Scanning Electron Microscopy (SEM)

The changes occurred due to milling can be observed in the scanning electron micrographs in figure IV. The micrograph of ATR showed irregular shaped particles with rough surface. After milling it alone, drug was reduced to smaller size, rough surfaced particles which adhered to each other forming agglomerates. It was clear from micrographs of physical mixture that, drug and superdisintegrant morphology was retained and some of the fine drug particles were seen dusted onto the fibers of CCS with little mixing into each other. The micrograph of co-ground mixture showed that co-grinding caused a reduction in particle size of ATR and confirmed the change in morphology of both the drug and superdisintegrant. Also, it was found that ATR and superdisintegrant are intimately mixed with each other.

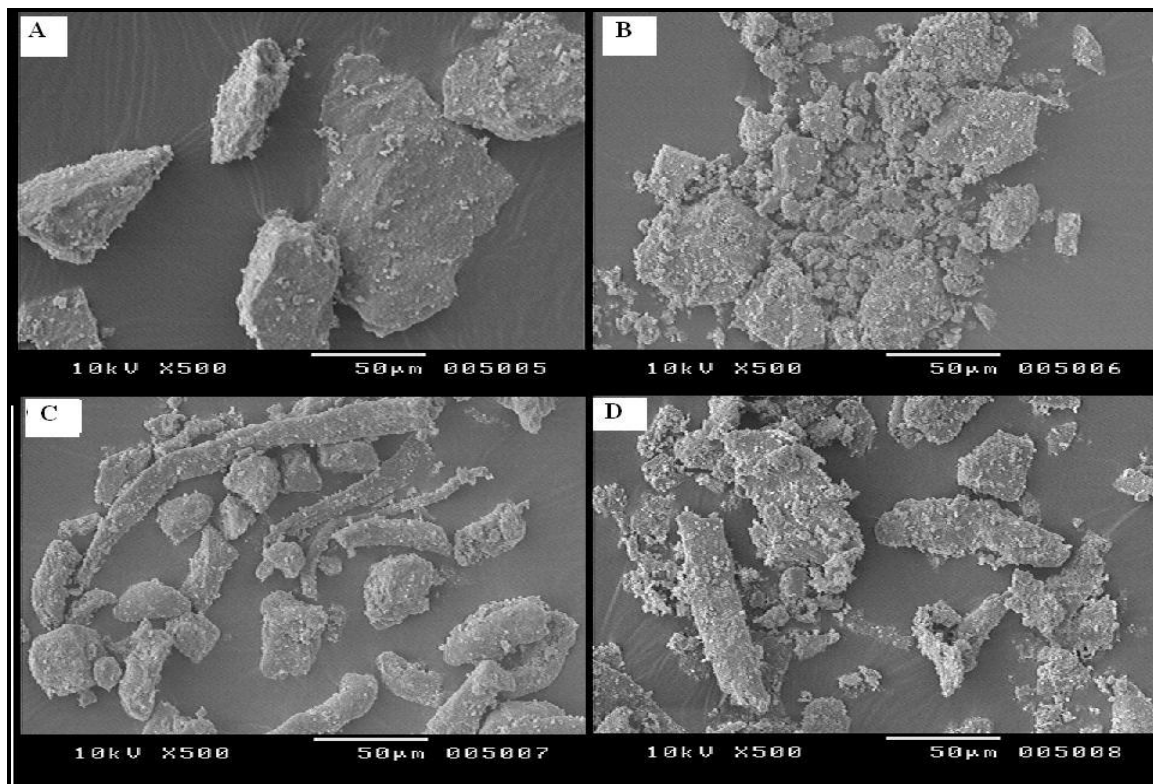


Figure 4: Micrographs (500X magnification) showing A: pure Atorvastatine calcium (ATR), B: milled Atorvastatine calcium (ATR), C: physical mixture and D: Optimized co-ground mixture.

Saturation solubility of prepared co-ground mixtures

The study (figure 5) showed that, ball milling of drug alone was not much useful for its solubility improvement as saturation solubility was found to be increased in all cases of co-ground mixtures than pure drug and drug milled alone. XRD, DSC and SEM studies proved reduced drug crystallinity, significant size reduction and intimate dispersion of drug and superdisintegrant particles after co-grinding. On the contrary, when drug was milled alone, it creates hydrophobic surfaces that tend to agglomerate with one another. This can lead to problems of solubility and stability [18, 19]. Hence, enhanced saturation solubility of co-ground mixtures may be attributed to amorphisation, larger surface area available for solubilisation due to size reduction of drug and availability of rich hydrophilic environment in its vicinity because of high water uptake capability of superdisintegrants.

As the ratio of superdisintegrant in co-ground mixture was increased from 1:1 to 1:3, solubility of the drug was found to be increased. Co-ground mixtures prepared with CCS showed highest solubilities than that with SSG and CP. Solubility was found considerably increased about 4 times in case of drug to CCS in ratio 1:3. It can be best explained on the basis of morphology and water uptake capacity of CCS [20, 21]. Because of typical morphological features of SSG and CP particles, they have less effect on solubility enhancement than CCS [22, 23].

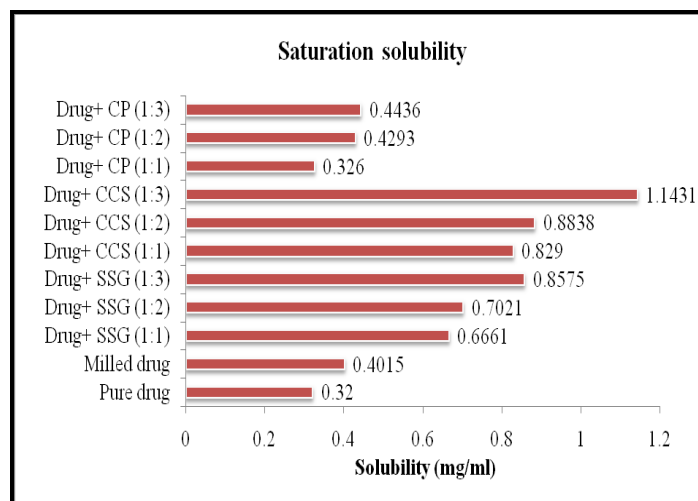


Figure 5: Saturation solubility of pure drug, milled drug and co-ground mixtures.

Flowability evaluation studies

Results of flow property evaluation are specified in table II. All the powder blends exhibited good flow properties, compressibility and distribution. The powder blends processed for compression into tablets.

Table II: Flowability parameters of powder blends.

| Batch | Angle of repose \pm SD | Compressibility Index (%) \pm SD | Hausner's ratio \pm SD |
|----------------|--------------------------|------------------------------------|--------------------------|
| Pure drug | 27.74 \pm 1.15 | 17.27 \pm 1.50 | 1.22 \pm 0.01 |
| Milled drug | 26.07 \pm 2.21 | 18.34 \pm 2.15 | 1.23 \pm 0.03 |
| F ₁ | 26.40 \pm 2.91 | 19.40 \pm 1.49 | 1.24 \pm 0.03 |
| F ₂ | 28.88 \pm 4.91 | 19.11 \pm 3.06 | 1.23 \pm 0.04 |
| F ₃ | 29.13 \pm 2.51 | 20.00 \pm 0.45 | 1.25 \pm 0.02 |
| F ₄ | 26.05 \pm 1.00 | 18.75 \pm 1.72 | 1.23 \pm 0.01 |
| F ₅ | 27.88 \pm 2.36 | 18.18 \pm 1.50 | 1.22 \pm 0.01 |
| F ₆ | 27.70 \pm 1.43 | 17.91 \pm 2.74 | 1.21 \pm 0.07 |
| F ₇ | 27.89 \pm 1.17 | 18.46 \pm 1.85 | 1.22 \pm 0.03 |
| F ₈ | 28.74 \pm 0.35 | 19.40 \pm 1.96 | 1.24 \pm 0.03 |
| F ₉ | 28.59 \pm 1.12 | 17.64 \pm 2.52 | 1.21 \pm 0.02 |

All values are mean \pm SD, n = 3.

Evaluation of tablets

Tablet evaluation results are depicted in table III. All batches of tablets were found to comply with the acceptance criteria as per IP 2007.

Table III: Evaluation of tablets.

| Batch | Weight variation* (mg) | Hardness (Kg/cm ²) | Friability (%) | Drug content (%) | In-vitro Disintegration Time (Sec) † |
|----------------|---------------------------|-----------------------------------|-------------------|---------------------|---|
| Pure drug | 128.16 ± 1.29 | 3.83 ± 0.28 | 0.61 ± 0.02 | 95.21± 0.45 | 49 ± 1.13 |
| Milled drug | 123.03± 1.77 | 3.63 ± 0.28 | 0.58 ± 0.05 | 98.00± 0.98 | 46 ± 0.73 |
| F ₁ | 125.18 ± 2.46 | 3.16 ± 0.28 | 0.55 ± 0.01 | 96.07± 0.12 | 67.66 ± 1.52 |
| F ₂ | 127.46 ± 1.12 | 3.00 ± 0.0 | 0.57 ± 0.04 | 97.01± 0.57 | 63 ± 2.0 |
| F ₃ | 126.34 ± 3.75 | 3.83 ± 0.28 | 0.54 ± 0.03 | 98.00± 0.98 | 61.66 ± 1.15 |
| F ₄ | 127.51± 2.74 | 3.00 ± 0.00 | 0.60 ± 0.03 | 97.90± 0.37 | 44.33 ± 0.57 |
| F ₅ | 125.43± 1.19 | 2.83 ± 0.28 | 0.61 ± 0.02 | 98.12± 0.22 | 39 ± 1.73 |
| F ₆ | 126.88± 2.98 | 3.63 ± 0.28 | 0.65 ± 0.08 | 99.4 ± 0.14 | 38 ± 1.0 |
| F ₇ | 128.35 ± 1.04 | 3.00 ± 0.00 | 0.58 ± 0.05 | 97.56± 0.28 | 57 ± 1.73 |
| F ₈ | 124.16 ± 3.23 | 3.83 ± 0.28 | 0.55 ± 0.06 | 96.14± 0.91 | 56.33 ± 0.57 |
| F ₉ | 126.46± 1.92 | 3.83 ± 0.28 | 0.59 ± 0.02 | 97.21± 0.45 | 53 ± 1.0 |

All values are mean ± SD, n = 3, * n = 20, † n = 6.

In vitro drug release

From dissolution study results (figures 6-8), it was clear that all the co-ground tablet formulation showed higher ($P < 0.05$) drug release than the tablets containing pure ATR (22.56 %) and milled ATR (41.77 %). There are two main reasons for dissolution enhancement. First, all the co-ground tablet formulation disintegrated rapidly due presence of superdisintegrants. Secondly, solubility of ATR was increased due to co-grinding. It is confirmed from XRD, DSC and SEM that co-grinding process has brought about changes at particulate level like particle size reduction, amorphisation and intimate mixture of fine drug particles with superdisintegrant. The rapid media uptake capacity of superdisintegrants worked favourably in dissolution enhancement. All tablets containing co-ground mixtures exhibited rapid initial drug release because of their rapid disintegration in dissolution media.

It is evident from the dissolution data that tablets containing co-ground system of drug and CCS exhibited higher dissolution (F_4 - F_6) than tablets containing co-ground system of SSG or CP. This was due to higher solubility and quickest disintegration of tablets containing co-ground mixture containing CCS into fine uniform particles [20]. Further, as ratio of superdisintegrant in co-ground system was increased from 1:1 to 1:3, respective drug release was also found to be increased ($P < 0.05$). This trend was observed in all superdisintegrants used. It may be because of increasing solubility and rapid disintegration of tablets with increasing superdisintegrant content.

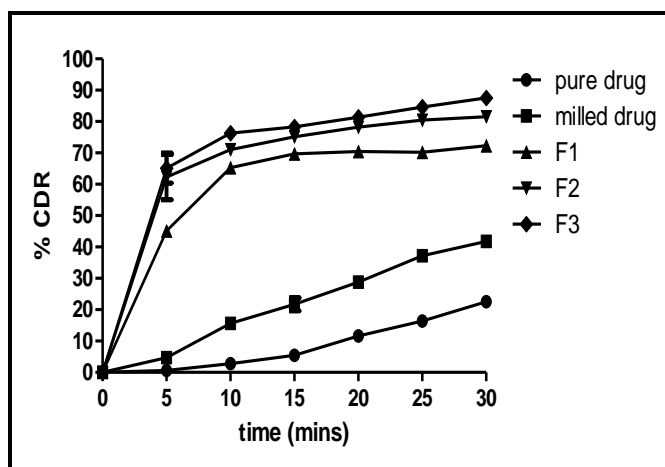


Figure 6: *In vitro* drug release profile of formulations F₁ to F₃ along with pure and milled drug formulation.

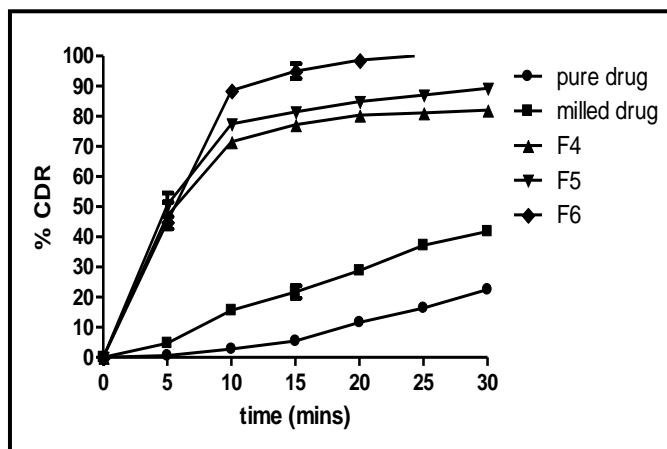


Figure 7: *In vitro* drug release profile of formulations F₄ to F₆ along with pure and milled drug formulation.

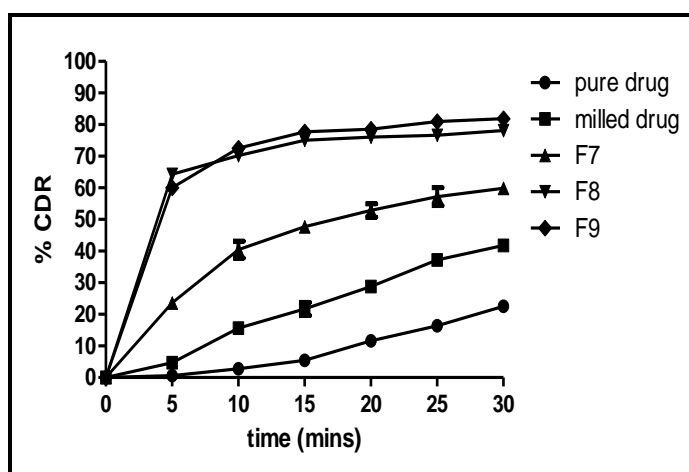


Figure 8: *In vitro* drug release profile of formulations F₇ to F₉ along with pure and milled drug formulation.

Selection of optimized formulation and comparison with marketed formulation

Amongst all formulation batches, tablets containing co-ground mixture of drug and CCS in ratio 1:3 (F₆) exhibited 100% release within 25 mins and excellent results of evaluation tests. Hence it was selected as optimized formulation. When its dissolution profile was compared with that of available marketed formulation of ATR, it proved that optimized formulation F₆ displayed superior drug release profile than marketed formulation. It can be observed in figure 9. F₆ had rapid initial release of about 90% in 10 mins and it was only about 47% in case of marketed formulation in same time. Within first 15 mins, drug release from F₆ was found significantly higher ($P < 0.05$) than marketed formulation.

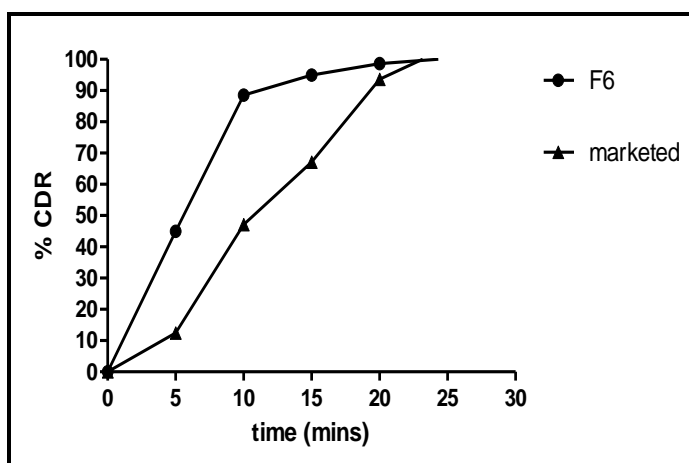


Figure 9: Comparative *in vitro* drug release profile of optimized formulations F₆ with marketed formulation.

CONCLUSION

Co-grinding of ATR with different superdisintegrants resulted in higher solubility and dissolution. CCS caused most enhancements in solubility and dissolution amongst all superdisintegrants tested. Co-grinding with CCS in the ratio 1:3 has showed promising results as it enhanced solubility of drug by about 4 times, which exhibited 100% *in vitro* drug release and better release profile than available marketed formulation. Wetting effect of superdisintegrants due to their high water uptaking properties, enhanced surface area available for solubilisation due to size reduction, amorphisation, and intimate mixing of drug with superdisintegrant were probable reasons for increased solubility and dissolution. It was evident that, as ratio of superdisintegrant was increased, solubility and dissolution also increased.

Thus, it can be concluded that co-grinding with superdisintegrants is an effective, simple and novel alternative to increase the solubility of BCS class II drugs and in future it will help to tackle bioavailability issues of other such drugs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

| | | |
|-------|---|--|
| ATR | - | Atorvastatine calcium |
| ANOVA | - | Analysis of Variance |
| BCS | - | Biopharmaceutics Classification System |
| CCS | - | Croscarmellose Sodium |
| CP | - | Crospovidone |
| DSC | - | Differential scanning calorimetry |
| GI | - | Gastrointestinal |
| FTIR | - | Fourier Transform Infrared |
| IP | - | Indian Pharmacopoeia |
| SEM | - | Scanning Electron Microscopy |
| SSG | - | Sodium starch glycolate |
| SD | - | Standard deviation |
| UV | - | Ultraviolet |
| XRD | - | X-Ray Diffraction |

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