Research Article

QBD BASED TERNARY SOLID DISPERSION OF ATORVASTATIN CALCIUM USING DIFFERENT APPROACHES

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ABSTRACT

Aim of the present work was to find out the best formulation technique for solid dispersion of poorly water soluble drug atorvastatin calcium using beta cyclodextrin (β -CD) and polyvinylpyrrolidone -K30 (PVP-K30) as polymers. The ternary solid dispersions were prepared using three different techniques that are, kneading, rotary evaporation and Spray drying. Two batches from each technique were prepared, with ratios of 1:1:1 and 1:1:2 for atorvastatin calcium, β -CD and PVP-K30 respectively. Prepared solid dispersions were characterized primarily for amorphization and drug polymer interactions by FTIR, DSC and SEM studies. From *in vitro* dissolution study, it has observed that dissolution of drug has been improved from all the employed techniques. Among all batches spray dried batches has shown greater drug release, hence selected for tablet formulation. From DSC and SEM characterizations it is predicted that there is an amorphization of drug which is mainly responsible for solubility enhancement. From FTIR study it has confirmed that some weak interaction forces like hydrogen bonding or hydrophobic interactions may be present. Overall results of spray dried solid dispersed batches were found better than all other batches, so spray drying technique has estimated better for dissolution enhancement of atorvastatin calcium.

Keywords: Atorvastatin calcium; β -cyclodextrin; Polyvinylpyrrolidone; Spray drying.

INTRODUCTION

In pharmaceutical development the lack of ability of a drug to go into the solution is one of most important constraint to its overall rate of absorption than its ability to permeate the intestinal mucosa, which ultimately leads to low bioavailability¹. Now a day's low bioavailability becomes major problem with more than 40% of the candidates in development pipeline because of high lipophilicity^{2,3}. To overcome this problem pharmaceutical development scientists have their scenario towards the approaches which efficiently enhance the solubility of poorly soluble drugs. Different strategies has been employed to improve the dissolution characteristics of poorly water soluble drugs like solubilization, pH adjustment, cosolvency, emulsification, self emulsification, polymeric modification, drug complexation, particle size reduction, amorphization, use of a surfactant as a solubilizing agent, liquid compact formation, the pro-drug approach and salt formation's etc^{4,5,6}. Amongst these the most promising method for enhancement of solubility and dissolution is the formulation of solid dispersion, because with solubility enhancement, solid dispersion have many other advantages like particle size reduction, molecular level distribution, improvement of wetting properties, porosity enhancement and stability enhancement^{7,8}. At present many new techniques have been developed for the preparation of solid dispersion and all these techniques have some advantages and disadvantages over the others^{9,10}. In accordance with the above scenario of solubility enhancement, in present work we have studied the effect of different solubility enhancement techniques on solid dispersion formulation of same polymers and at same ratio. The techniques which we have used in this work were kneading, rotary

evaporation and spray drying^{10,11}. Among these techniques we assessed that spray drying is one of most advantageous, because it produces very fine particles < 150 μ m and does not required additional milling process converts crystalline form to amorphous one highly soluble form and homogenous dispersion of drug in the carrier^{12,13}. Drug candidate which we have selected for the study was atorvastatin calcium (ATV) because it belongs to BCS class II drugs (low solubility and high permeability). ATV is a selective, competitive inhibitor of the 3-hydroxy methyl glutaryl coenzyme A (HMG-CoA) reductase enzyme that is involved in the conversion of HMG-CoA to mevalonate (a precursor of sterols, including cholesterol). It is very slightly soluble in water, freely soluble in methanol and practically insoluble at pH 4 and below. ATV is rapidly absorbed after oral administration, with time to reach peak concentrations (T_{max}) within 1–2 hrs. The fraction absorbed (%) and absolute bioavailability of atorvastatin are approximately 30% and 12%, respectively. Dissociation constant and reported partition coefficient of atorvastatin calcium are 4.46 and 6.36. Atorvastatin calcium is crystalline in nature with melting point 158.4 -178.03 °C¹⁴⁻¹⁶.

Generally, solubility (S) of a solid solute can be expressed by considering the three basic quantities as follow;

$$S = f(\text{Crystal packing energy} + \text{Cavitation energy} + \text{Solvation energy}) \quad (1)$$

In solubilization of any crystalline solids mostly which having high melting point, first major hurdle is the disruption of crystal packing. A crystalline solid possess relatively higher crystal packing energy, as compared to an amorphous solid. But an

amorphous solid has low packing energy and no long-range order of molecular packing. By this property of the amorphous solid, an amorphous solid often exhibit higher solubility than a crystalline solid. Same idea has to be applied for the crystalline ATV i.e. we should convert it in amorphous form. So that low energy will require for solubilization^{17,18}. Through all this deliberation of ATV we aimed to formulate solid dispersions of ATV using three different methods as mentioned above and studied their effect on the physicochemical properties of ATV through characterizing solid dispersions by means of (Fourier transform infrared) FTIR, (Differential scanning calorimetry) DSC, (Scanning electron microscopy) SEM, solubility and *In vitro* dissolution studies^{19,20,21}.

MATERIALS AND METHODS

Materials: ATV, PVP-K30 and β -CD were gifted from R and D laboratory of Lupin Ltd., Pune. All other chemicals and solvents were of reagent grade.

Saturation solubility studies

Solubility studies of ATV were carried out according to Higuchi and Connors method. An excessive amount of drug had added in distilled water, methanol and in 0.1N HCL separately in conical flasks of 10 ml capacity followed by analysis of dissolved fractions after 48 hours using UV spectrophotometer at λ max 246 nm^{22,23}.

Phase solubility studies

The effects of β -CD and PVP-K30 on solubility of ATV were investigated by adding excess amounts of ATV in 25 ml of aqueous solutions containing increasing concentration of β -CD, ranging from 0.1 to 1%w/v. Then, another phase solubility has performed in β -CD solutions of same concentrations but with addition of 0.25% W/V PVP-K30 at every concentration. The suspensions were shaken at 25°C for 48 hrs and concentrations of atorvastatin calcium were analyzed spectrophotometrically at λ max 246 nm.

The apparent 1: 1 stability constant was calculated from the solubility data using the following formula:

$$K_{1:1} = \text{slope} / S_0 (1 - \text{slope}) \quad (2)$$

Where, S_0 is the intrinsic solubility of atorvastatin^{24,25}.

Preparation of ternary solid dispersion systems

Aiming to improve the dissolution behavior of atorvastatin calcium in gastric conditions, ternary systems of atorvastatin calcium with β -CD and PVP-K30 were prepared with two different molar ratios 1:1:1 and 1:2:1 by kneading, rotary evaporation and spray drying technique. All the prepared samples were stored in desiccated environment until further study^{26,27}.

Kneading technique

The calculated amount of ATV, β -CD and PVP-K30 were properly weighed, transferred to a glass mortar and triturated with a small volume of Water/Methanol (1:1 volume ratio) mixture. The slurry obtained was kneaded for 30 min and then dried under vacuum at room temperature in the presence of calcium chloride as a dehydrating agent. Water/methanol was used as wetting agents to achieve better interaction of ATV with CD's during the kneading process^{28,29}.

Rotary evaporation

The calculated amount of ATV, β -CD and PVP-K30 were properly weighed. Firstly ATV and β -CD were appropriately dissolved in equal quantities of methanol and water, and then

aqueous solution of PVP-K30 was added to the above mixture. The solvent was removed under vacuum in a rotavapor (Veego India) at 90°C and 75 rot/min. The resultant solid dispersion was pulverized using a mortar and pestle, passed through a 250- μ m sieve (mesh size 60)^{30,31}.

Spray drying

The calculated amount of ATV, β -CD and PVP-K30 were properly weighed. At start ATV and β -CD were appropriately dissolved in equal quantities of methanol and water, then mixed together and aqueous solution of PVP-K30 were added to the above mixture. The above suspension was spray dried (LSD-48 mini spray dryer of JISL Pvt. Ltd.) from nozzle size of 0.7mm at 98-100°C and 47-49°C inlet and outlet temperatures respectively with feed rate 10 ml/min at atomization air pressure 2kg/min and aspiration 40.^{32,33,34}

Physicochemical characterization of prepared solid dispersion systems

Differential scanning calorimetry (DSC)

Prior to DSC analysis, a baseline was obtained which was used as a background. DSC analyses of samples were carried out on DSC S-650 (Universal V2.4F TA instruments. Samples (3–4 mg) were accurately weighed and sealed in aluminum pans and heated at a rate of 5°C/min. The measurements were performed at a heating range of 40–200°C under a nitrogen purge. A nitrogen flow rate of 20 ml/min was used for DSC run. All samples were analyzed in duplicate^{35,36}.

Scanning electron microscopy (SEM)

The morphology of samples was determined using scanning electron microscope (SEM) (HITACHI S-3000N, Japan), operated at an accelerating voltage of 20 kV (filament current of 1.75 IA, beam current of 30–40 mA and probe current of 250 pA). Samples were prepared by mounting 0.5 mg of powder onto a 5 mm X 5 mm silicon wafer affixed via graphite tape to an aluminum stub. The powder was then sputter-coated for 40 s at beam current of 38–42 mA with a 200 Å layer of gold/palladium alloy^{37,38}.

Fourier-transform infrared spectroscopy (FT-IR)

The infra red spectra of solid dispersions were recorded by the KBr method using a Fourier transform infrared spectrophotometer (FTIR-8400s). A base-line correction was made using dried potassium bromide and then the spectrum of the pure ATR, solid dispersions were obtained. A resolution of 2 cm⁻¹ was used and 64 scans were co-added for each spectrum over a frequency range of 4000–650 cm⁻¹. All samples were analyzed in duplicate^{39,40}.

Evaluation of drug content from solid dispersion systems

Solid dispersions equivalent to 10mg of ATV, prepared by each method were weighed accurately then dissolve with methanol and the drug content was UV-spectrophotometer (UV-1240, Shimadzu, Japan) assayed at 246 nm⁴¹.

In Vitro Dissolution studies of ATV solid dispersion systems

Dissolution studies were performed in triplicate using USP dissolution apparatus II for all the solid dispersion batches. Dissolution was performed in 900ml 0.1 N HCl at paddle speed 50 RPM and 37°C $\pm$ 2°C for 60 minutes. Samples (5 ml) were withdrawn and filtered (Whatman filter paper No. 41), diluted with dissolution medium and the percentage of drug release was spectrophotometrically assayed at 246 nm. The initial volume was maintained by adding 5 ml of fresh dissolution medium^{42,43}.

Preparation of ATV fast dissolving tablets:

Fast-dissolving tablets were prepared according to the proportions given in Table 2. The raw materials were passed through a 40-mesh screen before mixing. A powdered 1:1:2 solid dispersion containing an amount of ATV equivalent to 10 mg was mixed with the other excipients and directly compressed on a rotary tablet machine using 5mm diameter flat-face round punches (Accura, Ahmadabad). The tablet weight was adjusted to approximately 100 mg.

Experimental design of ATV fast dissolving tablet

A 3^2 randomized full-factorial design was used to examine the combined effect of formulation variables. In this design, two factors were assessed, each at three levels, and experimental trials were performed at all nine possible combinations. The amounts of superdisintegrant i.e. croscarmellose sodium (X1) and adsorbent Neusilin US2 (X2), were selected as independent variables. Disintegration time, friability and hardness were selected as dependent variables (response, Y).

Physical evaluations of prepared fast dissolving tablets

As shown in Fig.6 prepared fast dissolving tablets were tested for thickness, diameter, hardness, weight variation, and friability and disintegration time.

In vitro dissolution studies of prepared fast dissolving tablets

Dissolution studies were performed in triplicate using USP dissolution apparatus II. Dissolution of the tablets of optimized solid dispersion batch was compared with marketed tablets. Dissolution was performed in 900ml 0.1 N HCl at paddle speed 50 RPM and $37^\circ\text{C} \pm 2^\circ\text{C}$ for 60 minutes. Samples (5 ml) were withdrawn and filtered (Whatman filter paper No. 41), diluted with same dissolution media and drug content was spectrophotometrically assayed at 246 nm. The initial volume was maintained by adding 5 ml of fresh dissolution medium^{42,43}.

RESULTS AND DISCUSSION**Saturation solubility studies**

The solubility of ATV was found to be 68 $\mu\text{g/ml}$ and 52 $\mu\text{g/ml}$ at 25°C which is in good agreement with reported value of V.Sonje and L.Kumar, who found that aqueous solubility of ATV at 25°C is 23 $\mu\text{g/ml}$ ¹⁶.

Phase solubility studies

After performing phase solubility study of ATV in aqueous β -CD and β -CD-PVP-K30 solutions, we found A_L type of curve for both the solutions according to Higuchi and Connors. This indicates formation of one-to-one complex of drug and β -CD. We also found that solubility of atorvastatin calcium was linearly increasing as β -CD concentration increases as shown in fig.1. The solubility of atorvastatin calcium was increased from 68 $\mu\text{g/ml}$ to 958.2 $\mu\text{g/ml}$ at 0.8% of β -CD concentration and the stability constant value of ATV- β -CD complex was found to be 46.1 M^{-1} . After adding 0.25% solution of PVP-K30 to the above aqueous β -CD solution, the solubility of ATV and stability constant of the complex were increased significantly than β -CD alone. The values obtained were 987.80 $\mu\text{g/ml}$ and 93.4 M^{-1} for ATV solubility and stability constant of the complex respectively. This increase in stability constant value indicates, addition of 0.25% of PVP-K30 to the ATV- β -CD complex makes it more stable. It is reported that addition of PVP-K30 also increases complexation

efficiency of β -CD but there was no significant increase in drug solubility.

In vitro dissolution studies of prepared solid dispersion batches

Fig 2. shows the dissolution profiles of all solid dispersion batches. The drug release from pure ATV was only 29.7% within one hour in 0.1N HCL, which suggest a strong need of dissolution enhancement for this particular drug. In general, all solid dispersion batches have shown more distinct dissolution profile than pure ATV. It has demonstrated previously that utilization of different preparation technique and water soluble polymer's like PVP, HPMC and CMC gives additional solubility enhancement effect on β -CD and drug- β -CD complex with enhancement in complexation efficiency of β -CD^{25,26}. All solid dispersion batches have shown better dissolution profile than pure ATV. This dissolution promoting effect may be due to exterior interaction between ATV- β -CD complex and PVP-K30 which leads to amorphization of drug and increased wettability which contribute in solubility enhancement²⁷. It is also noted that, enhancement of dissolution by increasing the molar ratio of β -CD due to its wetting effect (34). From fig. 2 it is observed that drug release from spray dried batches i.e. 97.4% (E) and 99.6% (F) was comparatively faster than kneaded and rotary evaporated batches i.e. 79.4 (A), 81.4 (B) and 84.2 (C), 89.5 (D) respectively. This may be because spray drying produces more fine particles ($< 120 \mu\text{m}$ and not required additional milling process) and promote close interaction of ATV and β -CD which gives better inclusion complexation and homogenous molecular level dispersion of drug in PVP matrix leads to amorphization of drug (highly soluble form)^{27,29}. But in case of kneading and rotary evaporation techniques dispersion of ATV- β -CD may be less intimate in PVP matrix.

Fourier-transform infrared spectroscopy (FTIR)

In order to study the possibility of an interaction between ATV, β -CD and PVP-K30 in solid state, information was gathered from FT-IR spectroscopy. From the structure's of these three components and from previous demonstrations it can be assumed that a possible interactions could occur between the hydroxyl (-OH), amine (-NH) and carbonyl (C=O) group's of ATV, hydroxyl (-OH) of β -CD and carbonyl(C=O) and hydroxyl (-OH) groups of PVP-K30. From Fig.3 that it has observed that absorption bands of ATV at 3365.5 cm^{-1} (-NH stretching), 3228.3 cm^{-1} (asymmetric -OH sreching) were overlapped by broad peak's of β -CD and PVP-K30 at 3401(-OH) and 3826.90 (H_2O) respectively^{28,29,30}. The absorption band at 1651 cm^{-1} (C=O) of ATV was unchanged in IR of batch C 1652 cm^{-1} and was shifted to 1659, 1661, 1665 for batch D, E and F respectively. Hence, there may be interaction between 1651 cm^{-1} (C=O) of ATV with 3401 cm^{-1} (-OH) of β -CD. This specifies inclusion of ATV in the cavity of β -CD^{32,33}. In IR Spectra of ATV, band at 3669.81 cm^{-1} (free -OH stretching) was also present which had not observed in the IR spectra's of solid dispersion batch, this may be because of conversion to anhydrous form of ATV. All the major peaks related to PVP-K30 remained unchanged with slight shifting in their positions; this indicates the absence of well-defined interactions between ATV- β -CD complex and PVP-K30. Thus from all these observations we could say that these three components are compatible with each other in solid dispersion's prepared by any of used technique's.

Table 1: Solid dispersions batches

Techniques	Ratio's in gm Drug:Polymer:Carrier	
	1:1:1	1:1:2
Kneading	A	B
Co-evaporation	C	D
Spray drying	E	F

Table 2: Percentage of ATV in the solid dispersion samples

Batches	A	B	C	D	E	F
% Drug content	97±0.17	101±0.38	98±0.8	96±0.28	99±0.56	98±0.23

Table 3: Ingredients used for preparation of ATV fast dissolving tablets

Ingredients/Properties	A1	A2	A3	A4	A5	A6	A7	A8	A9
Drug (solid dispersion) (mg)	32	32	32	32	32	32	32	32	32
Neusilin -US2 (mg)	8	6	4	8	6	4	8	6	4
Ac-Di-Sol (mg)	3	3	3	4	4	4	5	5	5
Avicel (MCC) (mg)	54	56	58	53	55	57	52	54	56
Mg Stearate (mg)	1	1	1	1	1	1	1	1	1
Talc (mg)	2	2	2	2	2	2	2	2	2
Total weight (mg)	97	99	96	101	98	97	102	97	98
Thickness (mm)	3.07	3.02	3.05	3.03	3.05	3.09	3.06	3.07	3.04
Diameter (mm)	4.9	4.7	5	4.6	4.9	4.8	4.7	4.9	4.7
Hardness (kg/cm ²)	3.8	3.6	3.4	3.9	3.8	3.6	3.9	3.7	3.6
Friability (%)	0.38	0.35	0.33	0.30	0.34	0.31	0.35	0.33	0.29
Disintegration time (sec)	263	259	251	231	242	230	201	197	204

Table 4: 3² Full factorial design layout

Batch	A ₁	A ₂	A ₃	A ₄	A ₅	A ₆	A ₇	A ₈	A ₉
X ₁	-1	-1	-1	0	0	0	+1	+1	+1
X ₂	+1	0	-1	+1	0	-1	+1	0	-1

Table 5: Selected levels and factors of 3² full factorial design

Level's Factor's	Low(-1)	Medium(0)	High(+1)
Ac-Di-Sol (X ₁)	3	4	5
Neusilin (X ₂)	4	6	8

Figure 1: Phase solubility diagram of ATV in the presence of β-CD and β-CD-PVP- K30 in distilled water at 25°C.

Figure 2: Dissolution profiles of ATV from their solid dispersion systems with β-CD and PVP-K30 in 0.1N HCL at 37°C± 2.

Figure 3: FTIR spectra of pure atorvastatin calcium (ATV), β -CD, PVP-K30 and ATV- β -CD-PVP-K30 solid dispersion batches.

Figure 4: DSC curves of pure atorvastatin calcium (ATV), Co evaporation (C, D) and Spray dried batches (E, F).

Figure 5: SEM images of pure atorvastatin calcium and its spray dried solid dispersion of batch F.

Figure 6: Comparative dissolution profile of prepared fast disintegrating tablet's with marketed tablets of Abbott and FDC (10mg).

Physicochemical characterization of prepared solid dispersion systems

Differential scanning calorimetry (DSC)

The DSC thermograms of pure ATV, PVP-K30 and solid dispersion batches are shown in Fig 4. The DSC thermogram of pure ATV shows an endotherm at 152°C corresponding to its melting point, which may be due to its Crystalline nature. A little broad endotherm at 97°C could be attributed to removal of water molecules, which indicates ATV was in hydrate form. Broad endotherm at 248°C may indicate decomposition of ATV. The DSC thermogram of PVP-K30 has shown the broad endotherm ranging from 70 to 130°C may be due to its extremely hygroscopic nature. When we perform DSC study, we supply thermal energy to solid dispersion powder above the Tg of the polymer, leads to softening of the polymer, which acts as solvent for the drug. The solubility of drug depends on its affinity towards the polymer. As drug is continues to dissolve in polymer it converts from crystalline to amorphous form, after reaching to melting temperature, remaining quantity of drug gets melt and we get the melting peak at low temperature³⁵. Polymer or solvent which dissolves the drug completely with no melting peak is considered as the ideal polymer or solvent. In the DSC thermograms of solid dispersion batches the melting endotherm of pure ATV at 152°C and endotherm for loss of water molecules at 97°C was disappeared. This indicates ATV has completely converted into amorphous form and transformed to anhydrous form after formulation into ternary solid dispersion^{26,37}. But still the DSC thermogram of spray dried batches E and F are clearer than rotary evaporated batches C and D. This indicates more

intimate contact between ATV, β -CD and PVP-K30 has occurred by spray drying.

Scanning electron microscopy (SEM)

From *In vitro* dissolution, FTIR and DSC studies it has found that spray dried batches has given good results, so by performing SEM characterization here we have confirmed the morphology of pure drug and solid dispersed particles of spray dried batch (F) as shown in Fig.5 image A shows the crystalline structure of pure ATV and image B shows the morphology of spray dried solid dispersion batch (F)^{37,38}. From these SEM images we can observe that ATV has no longer remain in crystalline form after formulation into spray dried ternary solid dispersion and drug particles had completely covered by β -CD and PVP-K30.

Evaluation of percentage drug content: Table 1. Indicates drug was homogeneously distributed in all solid dispersion batches.

Formulation and evaluation of fast-dissolving tablets of prepared ATV solid dispersions

For optimizing the quantities of superdisintegrant and adsorbent, preliminary trials were conducted as shown in table 4 and 5 using 3² full factorial designs. All the prepared tablets were characterized for weight variation, uniform thickness, diameter, hardness, friability and disintegration time as shown in table VI. The tablets of batch A₇, A₈ and A₉ has shown earlier disintegration i.e. 201 seconds, 197 seconds and 204 seconds respectively and hence selected for comparison with marketed tablets. Normally croscarmellose sodium requires more time to disintegrate and we cannot increase its quantity above 4% of total tablet weight to get early disintegration, whereas tablets

containing croscarmellose sodium and Neusilin -US2 have taken less time for disintegration. This may be because of large specific surface area and porous nature of Neusilin -US2, which gives synergistic disintegrating action with croscarmellose sodium. As Neusilin -US2, is having large specific surface area and porous nature it has ability to adsorb the drug on its surface and prevent the drug re-crystallization in tablet form in moist environment^{23,24}. It also observed that, Neusilin -US2 increases the hardness of tablets with croscarmellose sodium without altering disintegration time.

In vitro dissolution studies of prepared fast dissolving tablet of ATV solid dispersions

Fig.6 shows comparative dissolution profiles of prepared ATV tablets with marketed ATV tablets of Abbott and FDC in 0.1N HCL. As discussed previously the purpose behind utilization of superdisintegrant and adsorbent in combination is to give faster disintegration and rapid release of drug from dosage form^{35,42,43}. The % drug release from Abbott and FDC marketed tablets was 100% and 45.6% respectively for 10 minutes and from prepared ATV tablets it was not less than 75% for A₇, A₈ and A₉ batch at same time. After 20 minutes the % drug release was 99.6%, 48.7%, 92.8%, 98.7%, 97.2% for Abbott, FDC and prepared A₇, A₈ and A₉ batch tablet's respectively. This indicates prepared fast dissolving tablet of spray dried solid dispersion batch was having good dissolution profile.

CONCLUSION

From phase solubility studies it has found that the ATV- β -CD-PVP-K30 ternary complex is more stable than binary complex ATV- β -CD. From FTIR characterizations it has confirmed that there are no well defined interactions between ATV, β -CD and PVP-K30. But still some kind of interaction's like hydrogen bonding, hydrophobic or Van der Waals interaction's may present, which generally results from inclusion complexation. From DSC and SEM characterization's it has observed that drug has converted from crystalline to amorphous form which ultimately leads to solubility enhancement. Thus the components of formed ternary solid dispersion's are compatible with each other. From in vitro dissolution study it has found that the drug release from spray dried solid dispersion's batches (E, F) was faster than that of kneaded (A, B) and Co-evaporated(C, D) batches. This shows that spray drying technique is better than kneading and Co-evaporation technique. From comparative dissolution profiles of prepared ATV tablets and marketed tablets (Abbott and FDC) it has concluded that prepared ATV tablets has shown comparatively similar dissolution profile with marketed tablet of Abbott but better dissolution profile than marketed tablet of FDC.

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