OPTIMIZATION AND CHARACTERIZATION OF FAST DISSOLVING TABLETS OF CANDESARTAN CILEXETIL PREPARED FROM SPHERICAL AGGLOMERATES

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ABSTRACT

The primary objective of this study was to develop a rapidly dissolving tablet containing an antihypertensive drug, candesartan cilexetil (CAND). The research work focused on improving solubility and *in vitro* dissolution of drugs using spherical agglomeration technique. Spherical agglomerates of CAND were developed using PVPK-30 as polymer and dichloromethane as bridging liquid. A spherical agglomerate of CAND was used to formulate fast dissolving tablet (FDT) with different superdisintegrants like Crospovidone and Cross carmellose sodium. The prepared powder blend was evaluated for different pre-compression parameters like solubility, compressibility index, Hausner's ratio and flow property and post-compression parameters including *in vitro* dissolution study. The solubility of prepared agglomerates was found to be 0.15 to 0.91 mg mL^{-1}, and it was higher than the pure drug (0.00071 mg mL^{-1}). *In vitro* drug release study of optimized batch of FDT has shown 95.47 % of drug release. From the results, it was revealed that the prepared FDT using the agglomeration technique might be used to enhance the solubility and bioavailability of CAND to augment acute and chronic hypertension therapy.

Keywords: Dissolution, disintegrates, polymer, solubility enhancement

INTRODUCTION

Solid phase category of medicines administration is largest, convenient and preferred dosage form. It has more advantages compared to the liquid dosage form. The most recommended delivery route is almost always oral[1]. The complete absorption of orally delivered drugs occurs only when they exhibit sufficient solubility in the gastrointestinal tract, leading to significant bioavailability[2]. The medication in the dosage form is delivered and breaks up in the encompassing gastrointestinal liquid to proceed with simple absorption. The therapeutic response of the drug depends also on bioavailability and solubility[3]. Solubility is an important component in achieving the desired concentration of medication in systemic and pulmonary circulations. In the current scenario of new drug molecules, only 8% of candidates coming under BCS first class[1].

Kawashima et.al discovered a novel particle designing technique of spherical agglomeration. It's a molecule-designing method, by which, in a single step, crystallization as well as agglomeration are completed[4,5]. The process of crystallization changes the fine crystals into spherical agglomerates during continuous stirring. Formulated agglomerates further work on the compressibility, the flowability of drug fixing, which empowers direct tableting of medication rather than additional handling like blending, granulation, sieving and drying[6]. There are some limitations like addition of solvent, polymer, and disintegrants, which must be streamlined to get the high number of crystals with spherical shape. The running steps engaged with the course of spherical crystallization are a zone of flocculation, a zone of zero development, a zone of steady size, and a zone of quick development[7,8]. A change in solvent strategy was utilized in the readiness of agglomerates. For obtaining small-sized spherical crystals the temperature and rotational speed of the stirrer were kept constant and further drug was incorporated in soluble solvent. With the use of bridging liquid, small crystals are agglomerated[9]. As the rate of stirring increased, it reduced the intermolecular forces between the particles. A higher rate of stirring produces spherical-shaped agglomerates that are not so much permeable but rather more impervious to mechanical pressure. Porosity was reduced as solid concentration increased in the same process. Viscosity

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affects the size distribution of the agglomerates. Bridging fluid impacts the rate of agglomeration as well as the quality of the agglomerates. The disadvantage of this technique is- it gives yield in low amounts because the medication shows significant dissolvability in the crystallization solvent. This technique is not pertinent to drugs with water insolubility[9,10,17].

Creating new techniques for improving the bioavailability of molecules that have intrinsically low watery solvency is a major obstacle to formulating solid drug medicament[4,5]. All post-compression parameters need to be within the limit for the formulation of the tablet[6]. Currently, different advancements are available in powder-based formulation with different ease of application[7,8,16].

Fast-dissolving tablets (FDT) have different benefits over controlled-dose solid medicament. FDT has a quick onset of action and it requires minimum time to dissolve in gastric medium and further disintegrate[11,12]. Certain diseases require the same condition to treat and control the disease, like hypertension. Candesartan cilexetil (CAND) specifically blocks or inhibits the receptor site of angiotensin II, and angiotensin AT1 receptors. Results are visible on adrenal gland tissue and smooth muscle. CAND inhibits or blocks the angiotensin AT1-mediated vasoconstrictive and aldosterone-secreting effects of angiotensin II, and results in a lowering of blood pressure. CAND is a drug of choice for angiotensin AT1 compared to angiotensin AT2 receptor. Inhibition or blocking of aldosterone emission can increase the level of sodium and water production and lower potassium emission. The current work focused on improving the solubility as well as dissolution behavior of drugs by using a novel spherical agglomeration technique. Further, the agglomerate was targeted to assess the impact of several disintegrants in the prepared batches of FDT.

MATERIALS AND METHODS

Lupin Ltd., Aurangabad provided a free sample of the drug candesartan cilexetil (CAND). All other polymers, like Crospovidone, Cross carmellose sodium, microcrystalline cellulose, lactose and solvents were received from Research Lab Fine Chemicals, Mumbai.

FTIR spectroscopic study in drug and polymer

The IR absorption spectrum of plain CAND drug was taken and compared with standard absorption spectra. Similarly, absorption spectrum of PVPK-30 was taken. Then, spectra of mixture of drug and polymer were taken and evaluated. Any interaction or bond formation in the main drug spectra and polymer was studied by IR spectroscopy.

Differential scanning calorimeter (DSC) study of drug

To assess the thermal behavior, DSC of CAND molecule was performed. A sealed sample in an aluminum crucible underwent heating at 10 °C/min from 30 °C to 300 °C with a flow rate of 10 mL min^{-1}. A thermogram of pure CAND was recorded using METTLER DSC 30S, Mettler Toledo India Pvt. Ltd.

Formation of spherical CAND agglomerates

Accurately weighed 1 g of drug CAND was dissolved in 50 mL of ethanol; this mixture is considered mixture 'A'. PVPK-30 was dissolved in 40 mL of water. This mixture is considered as mixture 'B'. The mixture B was poured in mixture A, after complete polymer miscibility in water. Then bridging liquid (dichloromethane 10 mL) was added to the above prepared complex mixture. This complex mixture was stirred for 30 min using mechanical stirrer Remi RQ-124. The agglomerates formed were filtered and dried at normal temperature for 24 h. To increase the yield, the same process was carried out for multiple times. The concentration of ingredients taken for preparation is shown in Table I.

Table I: Formulation of spherical agglomerates

Sr. No.	Ingredient	Quantity
1.	Candesartan cilexetil	1 g
2.	Dichloromethane	10 mL
3.	Methanol	50 mL
4.	Polyvinyl pyrrolidone	1 g
5.	Water	40 mL

Micromeritic evaluation agglomerates[13-15]

Angle of repose

It is defined the highest angle produced between the horizontal plane and the pile of powder. It is an indirect method to check the flow of powder. The results of the flow properties of the powder are described in Table II. The funnel method was used to measure the angle between the surface and the pile of powder.

Bulk density

It describes the mass-to-volume ratio of the powder. It is important to measure the bulk density as it is required for packaging the powder dosage form as well as a tablet, capsule-like dosage form. A cylinder with graduated dimensions was filled with accurately weighed 20 g powder, and the volume was accurately recorded. By applying a simple formula, bulk density was determined as:

$$\text{Bulk density} = \frac{\text{Mass}}{\text{Volume}}$$

Table II: Grading of powder flow property according to angle of repose

Angle of repose, degrees	Flow property
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Tapped density

It was carried out by weighing 20 g of powder filled in a graduated cylinder and tapping was carried out using tap density apparatus. The tapping procedure was done as per USP and the difference between initial volume and final volume was calculated to measure the tapped density.

$$\text{Tap density} = \frac{\text{Mass}}{\text{Tapped volume}}$$

Compressibility index

This method was employed to estimate powder flow properties. It directly measures the strength and stability of powder. The result of powder compressibility according to Carr's index is described in Table III and was determined by:

$$\textit{Carr's index} = \frac{\text{Tapped density–Bulk density}}{\text{Tapped density}} \times 10$$

Table III: Grading of compressibility of powder according to Carr's index

Carr's index	Flow property
5-15	Excellent
12-16	Good
18-21	Fair to possible
23-25	Poor
33-38	Very poor
>40	Excellent poor

Hausner's ratio

This ratio was used to predict the flow properties of powder. A ratio larger than 1.2 is recognized as having poor flowability. The standard ratio indicated less than 1.25 g mL^{-1} have good flowing property. It was estimated by the below formula.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Formulation of FDT of CAND agglomerates

Table IV describes the compositions of FDT with different excipients. From the above spherical agglomerates formulation, batch 2 was optimized and used for the preparation of FDT of CAND due to its good dissolution profile. Crospovidone and Cross carmellose sodium were used as superdisintegrants in tablets. Microcrystalline cellulose and lactose were used as binder and diluent, respectively. Magnesium stearate and talc were added as lubricants. All the formulation components were mixed properly. The prepared powder was directly compressed with the required hardness using a tablet punching machine.

Table IV: Composition of CAND fast dissolving tablet

Ingredient (mg)	F1	F2	F3	F4
Circular agglomerates	64	64	64	64
Crospovidone	13	20	-	-
Cross carmellose sodium	-	-	13	20
MCC	50	43	50	43
Lactose	67	67	67	67
Talc	3	3	3	3
Magnesium stearate	3	3	3	3

Post compression analysis CAND tablets[12,13]

Weight variation study

The test was done as per USP procedure by taking the weight of 20 tablets independently. The average weight of the tablet was taken and analyzed with the independent weight of the tablet. The percentage limit was compared with USP standards.

Friability

The weight of six tablets was taken and tablets were put in a Roche friability apparatus. All tablets were forwarded in the apparatus for rolling and consistent shocks, resulting in free fall from top to bottom through the paddle in the apparatus. As per the proceudre, revolution was carried out and weight was taken to measure the weight loss.

If the loss of weight of the tablet was below 1 % then it was considered and accepted. Percent (%) friability was calculated as follows.

$$\% \text{ Friability} = \frac{\text{Loss in weight}}{\text{Initial weight}} \times 10$$

Hardness and dimensions

The hardness of the tablets was evaluated using the Monsanto hardness tester. It was checked by compressing the tablet between anvil and piston. The dial reading was taken as the hardness of the tablet. Vernier caliper was used to determine diameter and thickness. Five randomly chosen tablets were taken from each batch, and the final reading was calculated using the average.

Wetting time

It relates to the contact time of dosage form with solvent. To know the disintegration properties, it is important to know the wetting time of FDT. Amaranth dye was mixed with 10 mL of purified water before being placed in a 10 cm diameter petri plate. The tablet was accurately placed in the middle of the petri plate and the required time for the solvent to pass at the upper layer of the tablet was measured as time of wetting. The same procedure was done for three times and the average was taken as the final reading.

Water absorption ratio

A petri dish having 6 mL water was taken with folded tissue paper. On the tissue paper, the tablet was placed. Complete wetting time for the tablet was noted. The same tablet was weighed and further ratio was determined by equation. The weights of the tablet before and after water absorption are indicated by the letters Wa, and Wb.

$$R = \frac{Wa - Wb}{Wb} \times 100$$

In vitro disintegration studies

The standard FDT shows disintegration in less than one minute. For evaluation of the time of disintegration, the individual tablet was placed in every tube of disintegration apparatus. The basket was filled with 1 L purified water and kept at 37 °C ± 2°C. The tablet was put to remain positioned at 2.5 cm below the surface of the liquid and not close to 2.5 cm from the bottom of the beaker during its upward and downward movement. The basket assembly was set and kept for movement at 28 to 32 cycles per minute. To comply with the standards of USP, the tablets

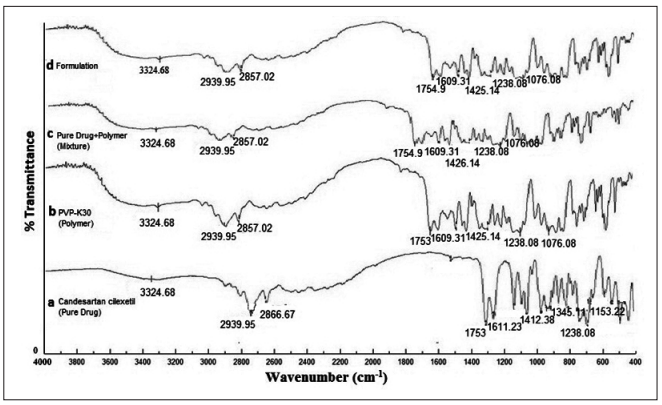

Fig. 1: FTIR of pure drug (CAND) (a), polymer (PVP K-30) (b), physical mixture (c) and formulation (d)

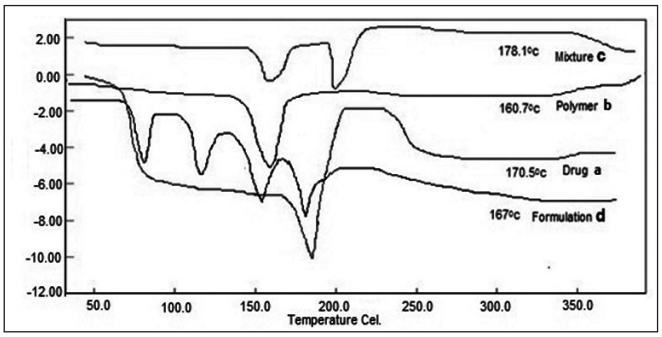

Fig. 2: DSC thermogram of pure drug (CAND) (a), polymer (PVP K-30) (b), physical mixture (c) and formulation (d)

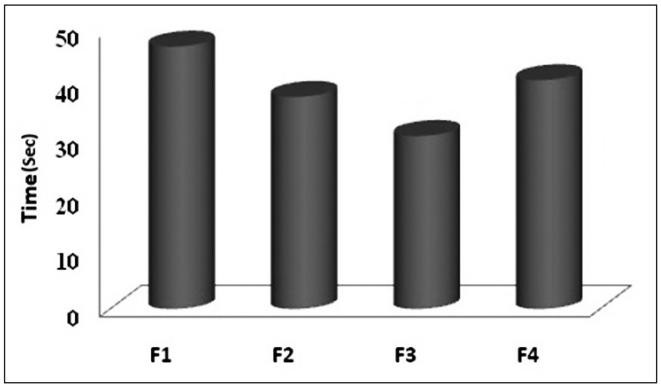

Fig. 3: Disintegration study of different formulation batches

Table V: Solubility of CAND in different solvents

Solvent	Solubility (mg mL^{-1})
Water	0.022
PEG 400	0.60
Acetone	1.80
Ethanol	2.70
Methanol	2.90

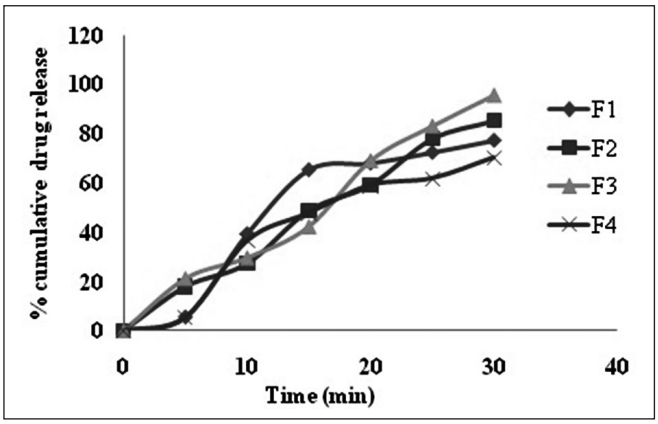

Fig. 4: % Cumulative drug release of formulation batches F1 to F4

should disintegrate and disintegrated particles should pass from the mesh of the basket in the expected time.

In vitro release studies of FDT of CAND

The dissolution study of the tablets was carried out on a USP type II apparatus using 900 mL of phosphate buffer solution pH 6.8 as dissolution medium, rotated at a speed of 50 rpm, and maintained 37 ± 0.50°C. After each 5 min intervals, 5 mL of sample was taken for analysis, filtered and diluted with dissolution medium, and analyzed at 257 nm using UV-spectrophotmeter.

RESULTS AND DISCUSSION

Determination of λmax CAND

After standard solutions, a concentration of CAND 10 µg mL^{-1} was taken and it showed high absorbance at a wavelength of 217 nm.

Compatibility study with PVPK-30

The Infrared spectrum of PVPK-30 is shown in Fig. 1. It shows C-H stretching vibrations at 2857.02 cm^{-1}, C = O carbonyl stretching at 1754.9 cm^{-1}, and C-N stretching vibrations at 1238.08 cm^{-1}. In a blend of PVPK30 and CAND, no changes were observed. The observation indicates the compatibility of CAND with the given polymer. The combined FTIR spectrum of PVP K-30 and CAND is shown in Fig. 1. From the compatibility study, it was observed that the mixture as well as formulation shows no more changes in the functional group.

Differential scanning calorimeter (DSC)

DSC graph of prepared agglomerates of the optimum batch was studied and revealed that there was a minor shift in the melting point of the blend because of the presence of polymer PVP K-30 and drug CAND. Fig. 2 indicates change due to the polymer and drug combination. DSC graph of pure drug CAND revealed a significant endothermic peak at 174.9 °C. It is the point at which pure drug melts. A differential scanning calorimeter was used to assess for any association between excipients and drugs. It additionally assists with finding the impact of temperature and pressure powers. DSC thermogram of polymer and combination is displayed in Fig. 2. The endothermic peak of CAND with a combination of polymers was acquired at 173.7 °C. The range of melting point of CAND is 160-175 °C. Spherical agglomerates of CAND show an endothermic peak at 167 °C indicating a reduction in the melting point of the drug i.e. drug is converted into amorphous form in a formulation. In this way, it suggests that the polymer and drug have a high degree of resemblance and true stability, and that temperature and pressure have no effect on drug stability.

Evaluation of FDT

Pre-compression evaluation of powdered mixture

Solubility of CAND was carried in different solvents which are shown in Table V. The powder mixture was assessed for precompression parameter. Powder blend flowability was considerably predicted to be good using the angle of repose. Table VI shows the findings.

Table VI: Pre-compression parameters of powder blend

Batch code	Bulk density (g mL^{-1})	Tapped density (g mL^{-1})	Compressibility index (%)	Hausner's ratio	Angle of repose (°)
F1	0.37± 0.03	0.40±0.05	7.5±0.01	1.081±0.02	21.1±0.12
F2	0.34±0.05	0.39±0.03	12.82±0.02	1.147±0.04	24.8±0.23
F3	0.36±0.04	0.43±0.04	16.27±0.03	1.194±0.03	26.4±0.17
F4	0.38±0.02	0.45±0.03	15.55±0.04	1.184±0.01	23.6±0.18

All values are taken in triplicates

Table VII: Post compression parameters of quick dissolving tablet of CAND

Batch code	Average weight (mg)	Hardness (kg cm^{-2})	Thickness (mm)	Friability (%)	Wetting time (sec)	Water absorption ratio	Disintegr-ation time
F1	194.3±0.002	2.5±0.1	4.1±0.1	0.102±0.002	61±0.00	52.2±0.03	47±0.21
F2	190.2±0.004	2.7±0.2	4.02±0.3	0.024±0.005	40±0.01	45.5±0.04	38±0.14
F3	197.0±0.007	3.0±0.1	4.1±0.2	0.081±0.007	75±0.00	64.4±0.05	31±0.3
F4	199.5±0.005	3.3±0.3	4.2±0.1	0.124±0.004	90±0.04	51.3±0.2	41±0.41

All values are taken in triplicate

Table VIII: Drug release profile of CAND FDT

Time (min)	F1	F2	F3	F4
0	0	0	0	0
5	5.6±0.002	17.81±0.01	21.09±0.002	5.6±0.001
10	39.37±0.005	27.18±0.002	29.53±0.04	36.56±0.01
15	65.39±0.004	48.75±0.001	42.18±0.003	47.81±0.03
20	68.04±0.001	59.06±0.003	68.9±0.001	59.06±0.002
25	72.42±0.03	77.81±0.02	82.96±0.02	61.87±0.001
30	77.31±0.02	85.12±0.03	95.47±0.01	70.26±0.04

Post-compression evaluation of FDT

All batches were forwarded to compress and test, compression parameters. The values were all within the accepted range for pharmaceuticals. Table VII contains a summary of the results for all batches and all parameters. The weight fluctuation of FDT in all batches was from 190.1 g to 199.3 g. All batches of tablets have the same reported thickness. Friability was tested and found less than 1 % friability, which indicates acceptable mechanical resistance for the tablets. The hardness of all batches was found in the range of 2.4 to 3.3 kg cm^{-2}. This indicates tablets have good mechanical strength. As per the standard requirement of FDT wetting time was found in a range of 40 to 90 sec.

Disintegration time

All batches shows less than 1 min disintegration time, which was 30 to 50 seconds as shown in Fig. 3. It was found that as the time of disintegration decreased, It could lead to an increase in the drug release. It was also noted from the result, that Crospovidone requires more time for disintegration time as compared to Cross-carmellose sodium.

In vitro dissolution study

The straight-line equation ($y = 0.057x + 0.031$, $R^2 = 0.977$) was used to calculate percent drug release. The pKa of the drug is 3.44, so the drug will be in unionized form and gets absorbed from the mouth. We have prepared a mouth-dissolving tablet, so pH 6.8 is used as simulated fluid for dissolving tablets in the mouth. The total percentage of drug release for batches F1 to F4 was seen to be 72.42 %, 77.81 %, 82.96 %, and 61.87 %, respectively at a time interval of 25 minutes. The maximum drug release obtained for batch F3 at 30 minutes was 95.47 %. Results of cumulative percent drug release were tabulated in Table VIII, and graphically represented in Fig. 4.

CONCLUSION

Spherical agglomerates of CAND were developed using PVP K-30 as polymer and dichloromethane as bridging liquid. The solubility of prepared agglomerates was found 0.15 to 0.91 mg mL^{-1}, and it was observed higher than the pure drug 0.00071 mg mL^{-1}. A spherical agglomerate of CAND was used to formulate FDT with different superdisintegrant like Crospovidone and Cross carmellose sodium. From the disintegration study of FDT, it was observed that Crospovidone requires more time for disintegration as compared to Cross carmellose sodium. From the *in vitro* drug release study batch F3 shown 95.47 % of drug release. From the results, it was revealed that the prepared fast-dissolving tablet using the agglomeration technique might be used to enhance the

solubility and bioavailability of CAND to augment acute and chronic hypertension.

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