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Original Article

EVALUATION OF INNOVATIVE CO-PROCESSED ADDITIVE FOR DIRECT COMPRESSION TABLETS USING ATORVASTATIN AND DIAZEPAM AS MODEL DRUGS

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ABSTRACT

Objective: The aim of the present study is to prepare and evaluate a co-processed excipient from commercially available Avecil PH102 and silicon dioxide colloidal (SDC) using direct compression technique for preparation of tablets.

Methods: The effect of the ratio of the two components on the properties of the prepared co-processed excipient has been investigated. In addition, it was evaluated for flowability, compressibility, and compatibility utilizing Fourier transforms Infrared (FTIR) and Differential scanning calorimetry (DSC) analysis. Tablets were produced by direct compression utilizing the co-processed additive with diazepam or atorvastatin calcium as model drugs in addition to magnesium stearate and talc as a lubricant. The addition of super disintegrant croscarmellose sodium or tablets preparation by wet granulation was utilized for comparison regarding the properties of prepared tablets. The prepared tablets were characterized for the drug content, hardness, friability, disintegration, dissolution, and stability.

Results: Optimal physicochemical properties of the excipient from a manufacturing perspective were obtained using a co-processed Avecil PH102-with SDC (2% w/w) to get a mixture. The FTIR and DSC analysis showed no chemical interaction. The properties of tablets made using co-processed excipient showed good hardness, friability, acceptable tablet disintegration time, dissolution rate, and stability comparable to that obtained by the multistep method of wet granulation. Although the addition of super disintegrant more shorten the disintegration time but the obtained value without croscarmellose sodium is still satisfied the requirement.

Conclusion: The Avecil PH102-SDC co-processed excipient produced was found to be promising as a valuable industrial, pharmaceutical excipient for the production of compressed tablets with good physical properties and fast dissolution.

Keywords: Low-cost excipient, Direct compressible, In situ prepared additives.

INTRODUCTION

Tablets and capsules are until yet a preferable oral dosage forms comparison to others because they provide accurate dose and high patient compliance, their large scale manufacturing is easy and economic [1]. The continuous researches in the last years for improving the properties of main components of tablets including the active ingredient and additives in addition to tablet machines retain the tablets as most desirable dosage form [2].

Although publications about direct compression are limited, but the lower number of steps and cheap procedure of direct compression in comparison to granulation method in addition to the production of new or modified additives move the focusing on this method and its components [3].

Co-processing is one of the approaches to improve the characteristics of additives the easiest and simplest method to modify the properties of two excipients to produce a new one with better quality for utilizing in direct compression of tablets [4, 5]. The compatibility and ratio of two excipients in the preparation of new co-processed excipient are of great importance in the determination of final properties of the new additive.

Since the co-processing is a physical change with no chemical intervention, thus it is more desirable than other approaches [6]. The aim of this work is in situ preparation of co-processed additive of low cost, good compressibility, uniform distribution, and simple in preparation in order to be a direct compression excipient alternative to the high-cost readymade excipient available in the market that used by many drug factories. Two model drugs, diazepam and atorvastatin calcium, belong to biopharmaceutical class I and II respectively were selected to incorporate in the tablets prepared using the new excipient to evaluate the application of excipient using the drug of different biopharmaceutical properties.

MATERIALS AND METHODS

Materials

Atorvastatin calcium and pure diazepam powder were supplied by Al-furat pharm industry, Iraq. Avecil PH102, SDC, and Croscarmellose sodium were supplied by Samara Drug Industries (SDI), Iraq. Talc and Mg stearate were obtained from BDH, England. All other materials utilized in the research were of pharmaceutical grade

Methods

Preparation of Co-processed avecil PH102-SDC

Four co-processed mixtures of Avecil PH102 and SDC at different SDC percent (1, 1.5, 2, and 2.5% w/w) were prepared.

The components of each mixture were sieved through 25 mesh No sieve, after that all components for 5 min mixed at 10 rpm utilizing a conical mixer machine (Erweka, Germany).

The mixture then was moistening with sufficient amount of water to achieve wet mass. After 15 min, through 60 mesh No sieve the wet mass was passed, and then dried for one hour at 50 °C.

Evaluation of the prepared Co-processed excipient

Angle of repose

Following the funnel method, the angle of repose of the prepared co-process powder mixture was determined. A funnel was stood over flat surface in a distance of 3 cm. The mixture was gradually poured through the funnel until the apex of the conical pile so formed just touched the tip of the funnel. The tangent of the angle was calculated using the following equation after measuring the radius and the height of the cone of the powders [7].

$$\text{Tan } \theta = \frac{h}{r}$$

Where θ is the angle of repose, h is the powder height, r is the powder radius. The standard values and their interpretation according to USP are shown in the table (1).

Compressibility (Carr's) index

An accurate weight of prepared co-process product mixture was poured into a graduated cylinder to measure volume initially (V_{in}) and then tapping was done until a constant volume was reached (V_f). The standard values and their interpretation according to USP are shown in table (2). The Carr's index was calculated using the following equation [8].

$$\text{Compressibility index} = 100X\frac{V0-Vf}{V0}$$

Fourier transform infrared (FTIR) spectroscopy

The Fourier transform infrared spectroscopy (FTIR) spectra were obtained using FTIR Shimadzu, Japan. Samples of a physical mixture of Avecil PH102 with SDC and optimum prepared co-process powder mixture were compressed with potassium bromide separately. The spectrum obtained was in range wave number of 4000-400 cm^{-1} [9].

Differential scanning calorimetry (DSC)

DSC can be used to determine the compatibility between drugs with an excipient and also used between two excipients. Thermal characteristics of samples of Avecil PH102, SDC, and optimum prepared co-process were determined by an automatic thermal analyzer system (Shimadzu DSC–60, Japan). Accurately weighed samples (2 mg) were placed in none hermetically aluminium pans and heated at the rate of 20 ˚C/minute against an empty aluminium pan as a reference covering a temperature range of 50 ˚C to 200 ˚C.

Preparation of tablets of model drugs

Table 3 shows the composition of tablets prepared using model drug either atorvastatin calcium or diazepam. All formulas prepared by direct compression method except formulas F4 and F7. The all components of formula except the lubricant were accurately weighed and passed through 60 mesh sieve. The powder was blended in a poly bag by tumbling for 15 min. The blending was continuing for further 1 minute after addition of magnesium stearate and talc as a lubricant. The mixture of powder was compressed using a 9-mm single punch tablet machine (TDP-6, China).

The tablets of formulas F4 and F7 were prepared by wet granulation method. The drug and other ingredients were mixed together except the lubricant, and then a specified volume of an ethanolic solution of Polyvinylpyrrolidone (PVP) (10% w/v) was added and mixed to form wet mass. The wet mass was granulated using sieve no. 10 and dried in a tray dryer at 65 °C for 10 min, and then re-granulated through sieve no. 60. The dried granules were then blended a poly bag with magnesium stearate and talc as lubricant for 1 minute and then compressed into tablets.

Table 1: The determination of flow properties in term of angle of repose

Angle of repose (θ)	flow
<25	excellent
25-30	good
30-40	passable
>40	Very poor

Table 2: Determination of flowability according to percent of compressibility

% of compressibility	Flowability
5-12	Excellent
12-16	Good
18-21	Fair passable
23-35	Poor
33-38	Very poor
>40	Very very poor

Table 3: Composition of tablets prepared to investigate the application of co-processed excipient

Ingredients (mg)	Formulas No.						
	F(1)	F(2)	F(3)	*F(4)	F(5)	F(6)	*F(7)
	Atorva-statin calcium	Atorva-statin calcium	Atorva-statin calcium	Atorva-statin calcium	Diaze-pam	Diaze-pam	Diaze-pam
Active ingredient	20	20	20	20	2	2	2
Prepared Excipient	170		165		122		
Lactose		170		166		122	120
Croscaremellose sodium			5				
PVP				4			2
Talc	8	8	8	8	4	4	4
Mg stearate	2	2	2	2	2	2	2
Total weight	200	200	200	200	130	130	130

Note: Formulas with star means prepared by wet granulation method

Evaluation of the prepared model drugs tablets

Weight variation

Randomly, twenty tablets were selected after compression and the mean weight was determined. None of the tablets should deviate from the average weight by more than±7.5%.

Uniformity of content

The content of diazepam was determined by High-pressure liquid chromatography (HPLC) method. Chromatography analysis was performed by Knauer HPLC system; the isocratic mobile phase consisted of buffer pH 3.4: Acetonitrile in the ratio of 55:45v/v at a

flow rate of 1.0 ml/min through C18 column (ODS, 25 cm ×4.6 mm, 5µ) was used as stationery phase. The detection wavelength for diazepam is 250 nm. Diazepam peak appeared at 5.65 min (fig. 1).

By appropriate aliquots of the standard diazepam solutions with the mobile phase, eight working solutions ranging between 10-80 µg/ml for diazepam were prepared. Each experiment was performed in triplicate according to optimized chromatographic conditions. The peak areas of the chromatograms were plotted against the concentration of diazepam to obtain the calibration curve with high correlation as shown in fig. (2) [10].

For determination of diazepam content in prepared tablets, twenty tablets were weighed, powdered and calculated the average weight of each tablet. Then the weight equivalent to 1 tablet was transferred into a 100 ml volumetric flask, 80 ml of diluent (mobile phase) added and sonicated for 25 min, further, the volume made up with diluents and inject the filtrate into HPLC system.

The content of Atorvastatin Calcium was determined by HPLC method. Chromatography was performed with Knauer HPLC system; the isocratic mobile phase consisted of Acetonitrile: 0.01M potassium dihydrogen phosphate solution in the ratio of 40:60 v/v adjusted to pH 4.0 with phosphoric acid at a flow rate of 1.0 ml/min through C18 column (ODS, 25 cm ×4.6 mm, 5µ) was used as stationary phase. The detection wavelength for the drug is 240 nm. Atorvastatin Calcium peak appeared at 6.39 min (fig. 3). By appropriate aliquots of the standard Atorvastatin Calcium solutions with the mobile phase, nine working solutions ranging between 0.1-0.9 µg/ml for Atorvastatin calcium were prepared. Each experiment was performed in triplicate according to optimized chromatographic conditions.

The peak areas of the chromatograms were plotted against the concentration of Atorvastatin calcium to obtain the calibration curve with high correlation as shown in fig. (4)[11].

For determination of Atorvastatin calcium content in prepared tablets, twenty tablets of Atorvastatin were accurately weighed and finely powdered. A portion of powder, equivalent to the weight of one tablet, was accurately weighed and transferred into 20 ml volumetric flask and 8 ml of mobile phase was added to it.

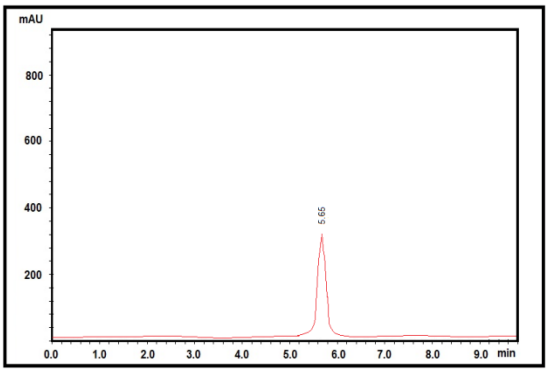

Fig. 1: HPLC chromatogram of pure diazepam

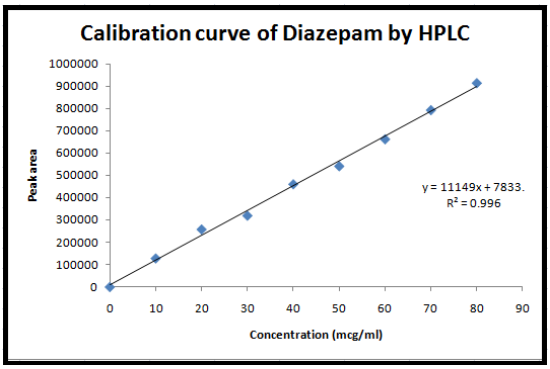

Fig. 2: Calibration curve of diazepam using HPLC method

The volumetric flask was sonicated for 20 min until there was complete dissolution of the atorvastatin. The solution was made up to mark with mobile phase and then filtered through a 0.45 µm millipore filter membrane to get sample solution which inject into HPLC system.

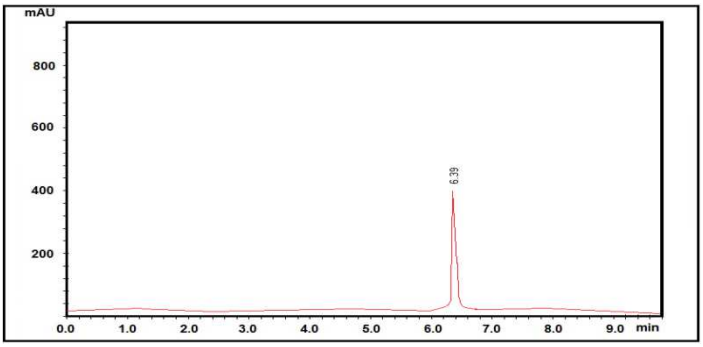

Fig. 3: HPLC chromatogram of pure atorvastatin calcium

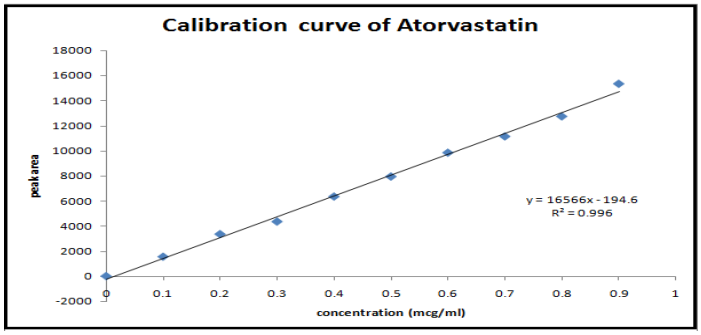

Fig. 4: Calibration curve of atorvastatin calcium using HPLC method

Hardness

The crushing strength of the tablets was measured using a Monsanto hardness tester. Three tablets from each formulation batch were tested randomly and the average reading±SD was recorded.

Friability

Twenty tablets were weighed and placed in a Roche friability tester and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out, dedusted and reweighed. The percentage friability of the tablets was calculated using the following equation [12].

$$\text{Percent friability} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \text{ X } 100$$

***In vitro* disintegration time**

Disintegration time (DT) of the model drug tablets were measured using a six station disintegration test apparatus (Disintegration Tester-USP, Electrolab, India) with disc according to the guidelines of British Pharmacopoeia. Distilled water

at 37±2 ℃ temperature was used as the disintegration medium. Six tablets of each brand were tested and the average disintegration time was calculated [13].

Dissolution studies

In vitro dissolution study of Atorvastatin Calcium was performed by using type II (paddle) dissolution apparatus (Copley, UK) at 80 rpm, and 900 ml of 0.1N HCL was used as dissolution medium. Six tablets of each formula were tested, one tablet in each of six vessels of the dissolution apparatus. The temperature of dissolution medium was maintained at 37±0.5 °C. Five ml aliquot of the dissolution medium was withdrawn at 45 min. Analysis of filtered solution was measured by HPLC method described in the section of determination of Atorvastatin calcium in tablets.

Dissolution of diazepam from prepared tablets was evaluated according to United States Pharmacopeia (USP) apparatus I using 900 ml of 0.1N HCL as a medium at 37 °C and 80 rpm. Six tablets of each formula were tested, one tablet in each of six vessels of the dissolution apparatus. Aliquot (5 ml) was withdrawn at 30 min. The sample filtered with 0.45 µm membrane filter, mixed with an equal volume of the mobile phase, and analyzed by the mentioned HPLC method [14].

Stability studies

Stability study was carried out on optimized formula. The tablets were stored at 40±2 °C/75±5 % RH for one year, and then the samples were evaluated for drug content by HPLC at the end of the study.

Statistical analysis

The mean±standard deviations of the experiments were calculated in addition to paired t-test was used in analysis at a significance level of $p \leq 0.05$.

RESULTS AND DISCUSSION

Directly compressible excipient can be prepared by many methods, one of them is the Co-processing. Co-processing of excipients could lead to the production of excipients with better properties than the pure individual excipient or the physical mixture of their components. Avecil PH102-SDC co-processed excipient was prepared at different mixing ratios of SDC relative to Avecil PH102. The results of flow properties of various batches of co-processed excipients at different mixing ratios are shown in table 4.

The results show that the angle of repose and Carr's index (CI) decreased significantly ($p<0.05$) as the content of SDC in the co-processed excipients increased until the optimum properties with 2% w/w SDC, above this percent there is no significant ($p>0.05$) improvement in flow properties. Although all batches of co-process excipient showed better flow properties than pure Avecil PH102, but co-processed excipient contains 2% w/w SDC consider the best among all batches of co-process excipients since it is showed excellent flowability according to pharmacopeia specification [15].

Table 4: The physical properties of different prepared co-process

Products	Average angle degree of Repose (°)	Compressibility Index (%)
Pure Avecil PH102 powder	31.5±0.7	33.0±0.90
Excipient contains 1.0% CSD	30.5±0.2	32.0±0.50
Excipient contains 1.5% CSD	29.0±0.4	28.0±0.30
Excipient contains 2.0% CSD	28.0±0.4	15.0±0.04
Excipient contains 2.5% CSD	28.0±0.3	14.7±0.03

Analysis of a physical mixture of Avicel PH102 with SDC by FTIR (Shimadzu FTIR 8000, Japan) shows a combination of characteristic peaks of both including peaks at 806.49, 1180.35, 1647.26, 2365.76, 3356.78 cm^{-1}which belong to Avicel PH102 while remaining peaks belong to the SDC as shown in fig. (5) and these results are in good agreement with that obtained by Chella Naveen *et al.* [16]. The appearance of main peaks in the physical mixture and optimum coprocessed excipients formulation as shown in fig. (6) Indicate the absence of chemical interaction between the two excipients.

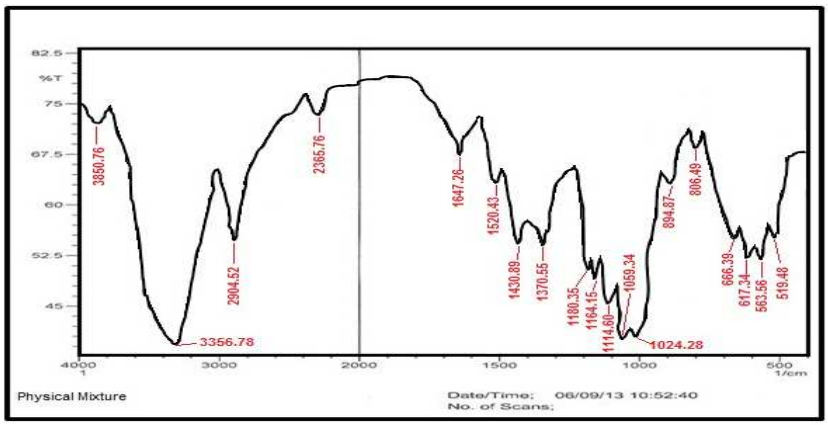

Fig. 5: FTIR spectrum of physical mixture of avecil PH102 with SDC

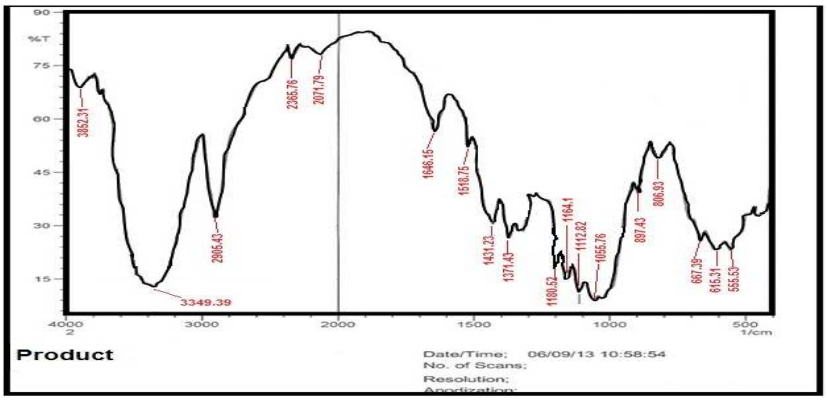

Fig. 6: FTIR spectrum of optimum prepared co-process excipient

The DSC thermogram of Avicel PH102 exhibited a broad endothermic peak at 80.70 °C that might correspond to the volatilization of adsorbed water as shown in fig. (7)[17]. The thermal behavior of SDC did not show any sharp peaks, revealing that this material was almost in an amorphous state as shown in fig. (8) [18].

The DSC thermogram of optimum co-processed excipients shown in fig. (9) Revealed a broad peak at 64.64°C differ than thermograms of pure excipients indicating that co-processed excipients technique led to the formation of new excipient with developed physical properties and this observation also recorded by Sanjay SP *et al.* [19].

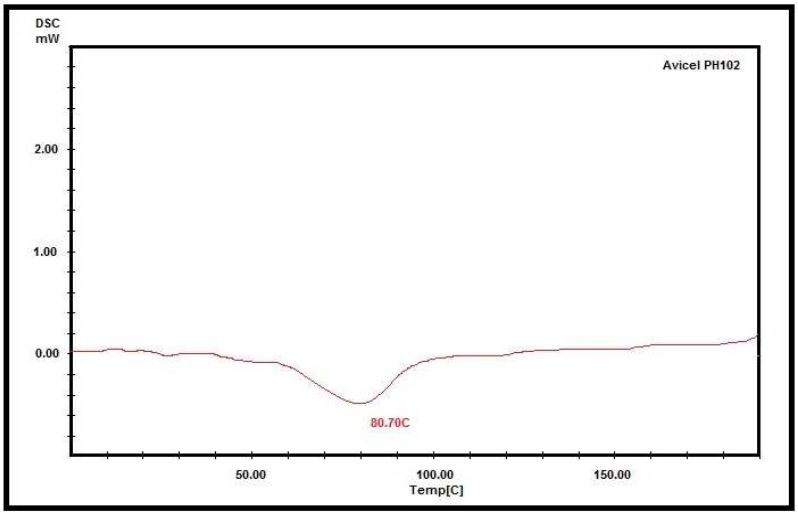

Fig. 7: DSC thermogram of pure avicel PH102

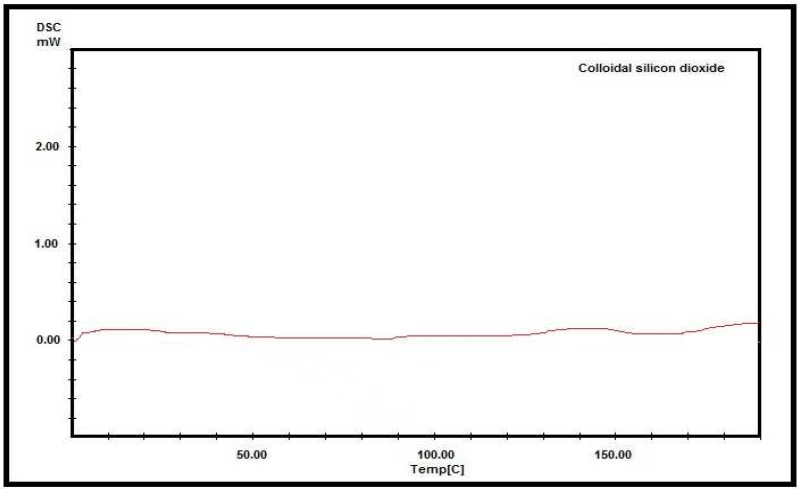

Fig. 8: DSC thermogram of pure SDC

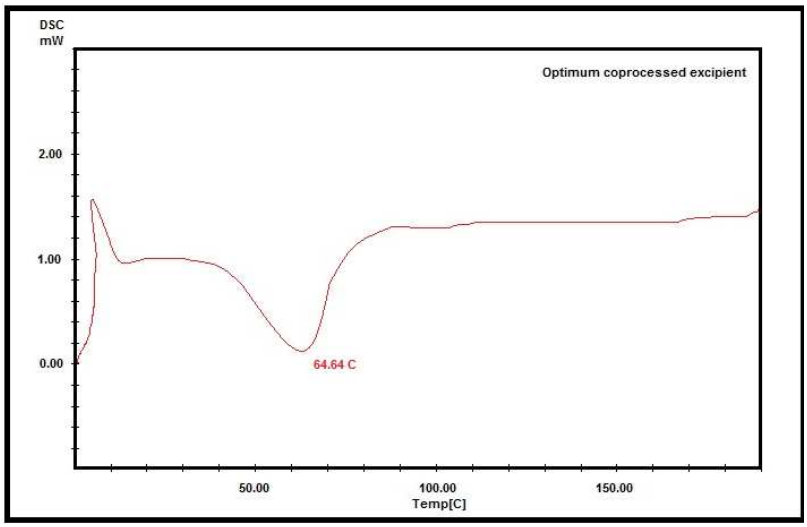

Fig. 9: DSC thermogram of optimum prepared co-process excipient

Analysis of evaluation parameters of prepared tablets as shown in table (5) indicates that co-processed incorporated tablet prepared by direct compression (F1 and F5) revealed better properties than that used lactose as excipient (F2 and F6) utilizing Atorvastatin calcium and diazepam as model drugs respectively, especially regarding high hardness, fast disintegration and dissolution.

Table 5: The evaluation parameters of the prepared tablets of model drugs

Formula	F1	F2	F3	F4	F5	F6	F7
Hardness (kg/cm^2)	6.5 ±0.02	2.6 ±0.007	5 ±0.03	6.5 ±0.03	6 ±0.05	2.7 ±0.01	7.5 ±0.04
Friability (%)	0.3 ±0.004	1.2 ±0.002	0.25 ±0.004	0.8 ±0.003	0.11 ±0.001	1.4 ±0.003	0.85 ±0.004
Disintegration time (sec)	60 ±0.9	55 ±0.7	30 ±0.2	360 ±1.3	40 ±0.7	38 ±0.4	420±0.3
Percent dissolved at specified time	95 ±2.4	98 ±1.7	97 ±1.2	78 ±3.2	98 ±1.3	99 ±1.5	85 ±1.6
Drug content (%)	100 ±1.9	99 ±1.3	100 ±1.8	97 ±1.2	100 ±1.1	98 ±1.5	95 ±1.9

Note: All values are mean of triplicate experiments±SD

In addition, comparable results were obtained relative to that tablets prepared by multistep wet granulation method (F4 and F7). Although the addition of super disintegrant in formula (F3) shows more enhancement in disintegration time, but still the impact of use the prepared co-processed excipients is significant and enough for good tablets properties requirements.

Stability study that carried out on optimized formulas (F1 and F5) indicates that there is no significant ($p<0.05$) changes in all properties of prepared tablets utilized the co processed excipients.

CONCLUSION

This work indicates that we can prepare the direct compression (DC) excipients immediately during the preparation of tablets batch without the need for commercial DC excipients of the high cost. In addition, the physical and chemical properties of manufactured tablets using the prepared excipients are of good performance with significant improvement in dissolution percent and stability of drug.

CONFLICT OF INTERESTS

Declared none

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