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ORIGINAL RESEARCH ARTICLE

Formulation, Evaluation & Optimization of Mouth Dissolving Tablets of Losartan Potassium: Effect of Co-processed Superdisintegrants

Shailesh Sharma*, Puneet Bhardwaj, G.D. Gupta

Dosage form Design Laboratory, Pharmaceutics Research Division,
Department of Pharmaceutics,ASBASJSM College of Pharmacy, Bela, Ropar Punjab, India.

ABSTRACT

Co-processing is defined as combining two or more established excipients by an appropriate process. Co-processing excipients could lead to formation of excipients with superior properties compared with the simple physical mixture component. Co-processed particles of Ac-di-Sol and Crospovidone were prepared using a solvent i.e. Isopropyl Alcohol, which were used as a direct compressible excipients in mouth dissolving tablet formulation. The two super disintegrates were mixed in varied proportion (according to 3^2 factorial design) by constant stirring until all the solvent was evaporated. The semi dried mixture of super disintegrates was passed through mesh screen size no. 60 and dried in tray dryer at 60°C. A two factor three level (3^2) factorial design is being used to optimize the formulation. Nine such different proportionate mixtures of superdisintegrants were prepared accordingly. The concentration of processed Superdisintegrants was then optimized for DT 35 secs. and friability 0.5% and used to formulate mouth dissolving tablet by direct compression method using other commonly used excipients and evaluated for disintegration time, wetting time, tablet hardness and percent friability. A decrease in disintegration time and wetting time was noted with tablet prepared by processed superdisintegrants when compared with tablet formulated using Ac-di-sol, Crospovidone alone; however there was no significant change in tablet hardness and percent friability.

Key Words: Mouth dissolving tablet, Co-processing, Factorial design, Losartan Potassium

INTRODUCTION

The oral route of administration still continues to be the most preferred route due to its manifold advantages including ease of ingestion, pain avoidance, versatility and most importantly patient compliance. The most popular dosage forms being tablets and capsules, one important drawback of these dosage forms however is the difficulty to swallow.[1]

Correspondig Author: Shailesh Sharma
E-mail: shailesh.bela@gmail.com
Contact No. 09888775589

To overcome these drawbacks, mouth dissolving tablets (MDT) or orally disintegrating tablets (ODT) has emerged as alternative oral dosage forms. These are novel types of tablets that disintegrate in saliva within few seconds of time[2]. According to European Pharmacopoeia, these should disperse/disintegrate in less than three minutes. The basic approach used in development of MDT is the use of superdisintegrants such as crospovidone, croscarmellose, sodium starch glycolate etc. that provide instantaneous disintegration of tablet after putting on tongue, thereby

releasing the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and due to pre-gastric absorption of saliva containing dispersed drugs that pass down into the stomach [3]. Moreover, the amount of drug that is subject to first pass metabolism is reduced as compared to standard tablets.

In recent years, scientists have focused their attention on the formulation of quickly dissolving/ disintegrating tablet. The task of developing rapidly disintegrating tablets is accomplished by using a suitable diluent and superdisintegrants. However formulation scientist have recognized that single component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately. Hence there is need to have excipients with multiple or combined characteristics. One such method is Co-processing [4].

Co-processing is defined as combining two or more established excipients by certain defined processes. Co-processing of excipients could lead to the formation of excipients with superior properties compared with simple physical mixture of their components or with individual components. As such the Co-processing of superdisintegrants is totally unexplored. The widely used superdisintegrants include Crospovidone, Croscarmellose sodium (Ac-Di-Sol) [5].

In present study, formulation, evaluation & optimization of mouth dissolving tablet of Losartan Potassium was done and studied the effect of co-processed superdisintegrants (prepared according to (3^2) factorial design) on the tablet disintegration time and percent friability. The drug of choice was Losartan Potassium because of novelty in its formulation as no Mouth dissolving tablet has been formulated. Losartan potassium is an effective antihypertensive drug and causes gastrointestinal disorders, neutropenia, acute hepatotoxicity, migraine and pancreatitis and low drug bioavailability. The low bioavailability would increase as the drug is directly taken in systemic circulation and first pass metabolism is avoided. [6-7]

MATERIALS AND METHOD

Materials

Losartan Potassium was gifted by Zydus Cadila healthcare Ltd., crospovidone, croscarmellose sodium and microcrystalline cellulose (MCC, PH-102), were gifted from signet chemical corp. pvt. Ltd. Lactose, dextrose, talc and magnesium stearate (analytical grade) were purchased from Loba Chem. Mumbai.

Methods

Preparation and evaluation of physical mixture and co-processed superdisintegrants

The physical mixture of the ac-di-sol and crospovidone was prepared by simple trituration technique of mixing using glass pestle and mortar. The co-processed superdisintegrants were prepared as follows: blend of various concentrations of superdisintegrants were prepared according to 3^2 full Factorial design and were added to 65 ml of isopropyl alcohol in a beaker (250 ml capacity), stirred on a magnetic stirrer while maintaining the temperature between 50-60°C till most of the isopropyl alcohol has been evaporated. The wet coherent mass was sieved through 60 mesh screen size and obtained powder was dried in a tray dryer at a temperature 60°C for 20 minutes. The dried powder was again sifted through 60 mesh sieve, packed and stored in dessicator for further use. The prepared physical mixture and co-processed superdisintegrants were evaluated for the mass-volume relationship, swelling properties and flow properties. Results were shown in **Table 1**.

Table 1: Formulation Table for Preliminary Batch

Ingredients	F1	F2	F3	F4	F5	F6	F7*	F8^
Ac-di-Sol	0.8	1.6	2.4	-	-	-	0.8	0.8
CP	-	-	-	0.8	1.6	2.4	0.8	0.8
Lactose	24.8	24.8	24.8	24.8	24.8	24.8	24.8	24.8
Dextrose	25.6	25.6	25.6	25.6	25.6	25.6	25.6	25.6
MCC	25.6	24.8	24	25.6	24.8	24	24.8	24.8
Talc	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
Mg. Sterate	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
Evaluations								
Hardness (kg/cm^2)	3.1 ±0.122	3.1 ±0.097	3.2 ±0.124	3.0 ±0.134	3.0 ±0.121	3.1 ±0.143	2.98 ±1.238	3.0 ±1.22
Friability (%)	0.412 ±0.025	0.465 ±0.023	0.526 ±0.054	0.311 ±0.032	0.339 ±0.053	0.456 ±0.014	0.582 ±.022	0.290 ±0.028
Wetting Time (seconds)	98 ±1.48	84 ±1.69	68 ±2.65	90 ±1.07	76 ±1.86	55 ±2.60	84 ±1.54	52 ± 1.15
Disintegration time (Seconds)	107 ±1.83	95 ±2.41	76 ±2.06	102 ±1.09	81 ±2.38	62 ±1.48	90 ±1.32	75 ±1.28

*physical Mixture (1:1), ^Co-processed, n=6

Preparation of Mouth Dissolving Tablets (Preliminary Batch)

Mouth dissolving tablets were prepared by direct compression technique. All the ingredients were passed through mesh screen no. 60 and weighed in geometrical order and the blend was then compressed into tablet. The tablets were prepared with superdisitegrant alone, physical mixture (1:1), co-processed superdisintegrants (1:1). The batch was shown in **Table 2**.

Table 2 Evaluation of Superdisintegrants

Code	Ratio (Ac-Di-Sol: Crospovidone)	Hausner's Ratio R_H±SD	Compressibility Index I_c±SD	Angle of Repose (^{0}) ±SD
Ac-Di-Sol		1.250±0.004	20.029±0.234	36.18±0.174
Crospovidone		1.494±0.034	33.039±1.519	44.02±1.010
Physical Mixture	1:1	1.299±0.039	22.946±2.268	37.83±1.714
Co-processed	1:1	1.122±0.004	10.856±0.332	24.42±0.626

(n=6)

Evaluation of Mouth Dissolving Tablets

Weight Variation for which twenty tablets were selected randomly from each formulation and weighed individually using a shimadzu digital weighing balance. The individual weigh of each tablet was compared

with the average weight for weight variation. Hardness of the tablet was measured using Monsanto hardness tester (Pharmalab, Ahmedabad, India) and the results were recorded. Percent friability of the sample of twenty tablets was measured using USP type Roche friabilator (Pharmalab, Ahmedabad, India)[6]. Preweighed tablets were placed in the chamber and the friabilator was set at 25rpm for 4 minutes. The tablet were then dusted, reweighed and percent weight loss (%Friability) was calculated and recorded. For wetting time tissue paper was folded twice and placed in the petridish having an internal diameter of 5 cm containing 6 ml of water. A tablet was placed on the surface of tissue paper. The time required for the water to reach the upper surface of the tablet is recorded as the wetting time[7]. A modified method was used to determine disintegration time of the tablets. A cylindrical vessel was used in which 10-mesh screen was placed in such way that only 2 ml of disintegrating or dissolution medium would be placed below the sieve. To determine disintegration time, 6 ml of Sorenson's buffer (pH 6.8), was placed inside the vessel in such way that 2 ml of the media was below the sieve and 4 ml above the sieve. Tablet was placed on the sieve and the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet. Six tablets were chosen randomly from the composite samples and the average value was determined. For the content uniformity test, ten tablets were weighed and grounded to fine powder, powder equivalent to drug content in formulation was extracted in distilled water and liquid was filtered through Millipore filter paper. The drug content was then determined from the standard plot obtained by measuring the absorbance of appropriate dilution at 204.5 nm on UV-Visible spectrophotometer. In vitro dissolution studies of the promising formulation was performed according to USP XXIII Type-II dissolution apparatus, employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37 ± 0.5°C as dissolution medium. Aliquots of the dissolution medium were drawn at specific time intervals and replaced immediately with equal volume of fresh medium. The samples were filtered through 0.22 membrane filter disc and analyzed for drug content by measuring the absorbance at 206.5 nm. Drug concentration was then calculated from standard calibration curve.

Factorial Consideration

The experimental design was 3^2 full-factorial design, and nine formulations were prepared. The amount of superdisintegrants X_1(Ac-di-sol) and X_2(Crospovidone) were selected as independent variables. The amount of superdisintegrants was optimized for dependent variables: disintegration time and percent friability. The low (-1), medium (0) and high (1) are the values of X_1(Ac-di-sol) and X_2(Crospovidone) respectively. All the possible nine batches were shown in **Table 3.**

RESULTS

In preliminary investigation, water, ethyl alcohol, dichloromethane, and isopropyl alcohol were used for co-processing of the superdisintegrants. Water was ruled out for further experiment because gel formation occurs in Croscarmellose sodium. Dichloromenthane was omitted because of floating of crospovidone and sedimentation of Ac-di-sol. From ethyl alcohol and isopropyl alcohol, isopropyl alcohol was chosen because Ac-di-sol is sparingly soluble in ethyl alcohol. Isopropyl alcohol was selected considering the absence of gel formation and phase separation.

Evaluation of Ac-di-sol, crospovidone, their physical mixture and co-processed of superdisintegrants

Table 1 reports the bulk density, tapped density, Compressibility Index (I_c) and

Hausner's Ratio for all studied batches. According to literature data powder with a I_c between 5 to 18% are suitable for producing tablets, and those with a Hausner's Ratio below 1.25 are exhibited good flow ability. Only co-processed superdisintegrants batch falls in the limit/range. On the evaluation of superdisintegrants angle of repose of the physical mixture and co-processed Ac-di-sol : Crospovidone (1:1) was found to be 38^0 and 24^0 respectively. According to USP, good flow (angle of repose between 20^0 and 30^0) was shown by co-processed superdisintegrants. Therefore, it was concluded that particle size distribution of the excipients would be kept the same to avoid the tableting problem that is dependent on the flow of powder from hopper to die cavity.

Table: 3 Factorial Design based Losartan Potassium MDT Formulation

Batch code	X_1 (mg.)	X_2 (mg.)	DT (secs.)	%Friability
FDT1	-1	-1	52	0.29
FDT2	-1	0	41	0.33
FDT3	-1	1	32	0.42
FDT4	0	-1	43	0.47
FDT5	0	0	36	0.53
FDT6	0	1	24	0.60
FDT7	1	-1	28	0.65
FDT8	1	0	22	0.71
FDT9	1	1	17	0.74
LMD	0.23	0.19	37	0.52

Coded values	Actual Values	
	X_1	X_2
-1	1	1
0	2	2
1	3	3

X_1 indicates amount of Ac-Di-Sol (mg); X_2, amount of Crospovidone (mg); DT, disintegration time; and F, friability.

Evaluation of preliminary trial batch

The preliminary trials were conducted by using 1 to 3% w/w superdisintegrants Ac-di-sol and crospovidone. On the basis of the results obtained in the preliminary screening studies, the batch containing Ac-Di-Sol and crospovidone showed the fastest disintegration in very high concentration but not to be 30 seconds and friability is also increased consequently. The results in **Table 2** clears that the disintegration time and percent friability have a great difference in physical mixture and co-processed superdisintegrants (Batch F7 and F8). The use of a physical mixture of superdisintegrants resulted in increased friability probably due to low compressibility of excipients. So by co-processing of Ac-di-sol and crospovidone may decrease the percent friability of the tablets. The result of preliminary examination revealed that tablets containing 1:1 physical mixture of Ac-Di-Sol and crospovidone showed a higher friability than that of tablet of co-processed superdisintegrants.

Evaluation of factorial batch

The results shown in **Table 3** indicate that concentration-dependent disintegration

was observed in batches prepared using co-processed Ac-di-sol and crospovidone. The absorption and swelling is responsible for faster water uptake; hence it facilitates wicking action of crospovidone in bringing about faster disintegration. It is worthwhile to note that as the concentration of Ac-Di-Sol is increased, the wetting time is decreased. Tablets with lower friability (≤ 0.6%) may not break during handling on machines and/or shipping. The response surface plots are shown in **Fig 1**. One of the primary requirements of immediate release preparation is faster disintegration. Considering these results, it may be concluded that co-processed superdisintegrants is superior to physical mixture for formulating the fast dissolving tablets. In order to investigate the factors systematically and optimize the tablet for DT 35 seconds and % F less than 0.6%, a factorial design was employed in the present investigation.

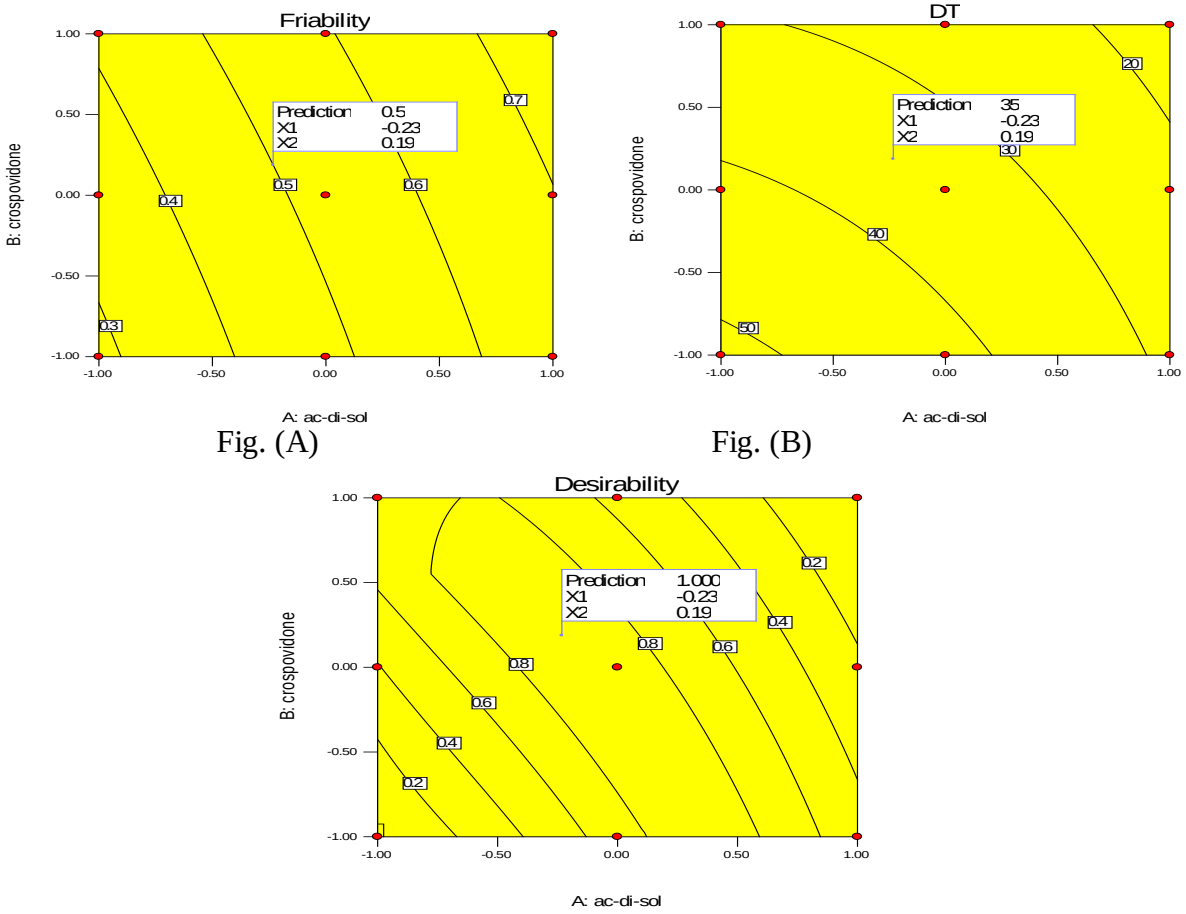

Fig. (A) Fig. (B)

Fig 1: Response Surface Plots for Friability, DT and Desirability

Optimization of the Fast Dissolving Tablet

The optimization of the fast dissolving tablet was decided to target disintegration time 35 second and percent friability is 0.6%. The optimized concentration was obtained by software as clears in the surface response prediction curves. Optimization results or coefficient values for disintegration and friability were shown in **Table 4**. A checkpoint batch LMD was prepared at X_1= -0.23 level and X_2 = 0.17 level. From the full model, it is expected that the friability value of the checkpoint batch should be 0.5, and the value of disintegration time should be 35 seconds.

Table 4: Coefficients for Polynomial Equation for Dependent Variables

Coefficient	b_0	b_1	b_2	b_{12}	b_1^2	b_2^2
DT	34.56	-9.67	-8.33	2.25	-2.33	-0.33
% Friability	0.53	0.18	-0.058	-0.010	-0.010	0.0005

Table 5 indicates that the results are as expected. Thus, we can conclude that the statistical model is mathematically valid. The drug release was at the end of 5 minutes was more than 90%.

Table 5: Evaluation of optimized Losartan Potassium MDT Formulation

Ingredients	Amount
Losartan potassium	25
Ac-di-Sol	1.77
Crospovidone	2.19
MCC	22
Lactose	12.92
Dextrose	12.92
Talc	1.6
Mg. Stearate	1.6
Parameters	**Results (LMD)**
Weight variation	80±8 mg
Friability	0.52 %
Disintegration time	37 secs
Wetting time	31 secs

DISCUSSION

Effect of Independent Variables on Dependent Variables

The results of multiple linear regression analysis reveal that, on increasing the concentration of either Ac-Di-Sol or crospovidone, a decrease in disintegration time is observed; both the coefficients b_1 and b_2 bear a negative sign. When higher percentage of Ac-Di-Sol is used, higher water uptake swelling and deformation of the Ac-Di-Sol take place, which gives internal pressure to tablet to disintegrate due the swelling of the disintegrants. The water uptake and subsequent disintegration are thus facilitated. It is obvious that in the presence of higher percentage of superdisintegrants crospovidone, wicking is facilitated.

An increase in the concentration of Ac-Di-Sol leads to an increase in friability because the coefficient b_1 bears a positive sign. When a higher percentage of Ac-Di-Sol is used, low compressible tablets are produced, which are mechanically weak. The increase in the concentration of crospovidone results in decreased friability values because b_2 bears a positive sign. Crospovidone is known to produce mechanically strong tablets.

CONCLUSION

Co-processed superdisintegrants consisting Ac-di-sol and crospovidone exhibited good flow and compression properties. The results of a 3^2 full factorial design revealed that the amount of Ac-di-Sol and crospovidone significantly affect the dependent variables, disintegration time, and percentage friability. It is thus concluded that by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts.

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