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Original Article

Design, Development and Evaluation of Isosorbide Mononitrate Orally Disintegrating Tablets

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ABSTRACT

The present study was carried out to develop oral disintegration tablets of Isosorbide Mononitrate. The formulations were prepared by direct compression technique using different super disintegrants such as Ac-Di-Sol, Poly Plasdone Xl, and Tulsion 339. The drug –excipients compatibility study was done by FTIR and DSC. The prepared blend of all the formulations were showed good flow properties such as angle of repose, bulk density, tapped density. After compression, the tablets were evaluated for thickness, hardness, friability, weight variation, disintegration and dissolution test as per I.P. and showed results within the range. Among all the formulations F9 formulation was showed maximum % drug release i.e., 88.68% in 30 min and it is considered as optimized formulation.

Keywords: Isosorbide Mononitrate, Oral disintegrating tablets, direct compression

1. INTRODUCTION

The oral route administration is most preferred route due to ease of administration, avoidance of pain, versatility and is administered in the form of both solid dosage forms and liquid dosage forms. A pill can be designed for swallowing or chewing to deliver a precise medication dose to the patients [1]. Under moderate pressure, the pills including tablets and capsules are able to retain their shapes. The disadvantage of this route is the difficulty in swallowing or

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chewing solid dosage forms particularly in pediatric and geriatric patients. Due to fear of throat choking many pediatric and geriatric patients are unwilling to take these solid preparations. In order to overcome the difficulties associated with this system of administration, several fast dissolving drug delivery systems have been developed [2,3]. By using variety of technologies, including direct compression, wet granulation and freeze-drying the fast dissolving drug delivery systems can be manufactured [4].

Isosorbide mononitrate is a nitrate-class drug used for the prophylactic treatment of angina pectoris; that is, it is taken in order to prevent or at least reduce the occurrence of angina. Research on isosorbide mononitrate as a cervical ripener to reduce time at hospital to birth is supportive [5].Isosorbide mononitrate film formulation is useful for bedridden and geriatric patient with Angina pectoris who are unwilling to take solid dosage form. Hence an effort was taken to formulate Isosorbide mononitrate as a oral disintegrating tablet [6].

In the oral administration of drugs, the drinking water is mostly required, like tablet and capsules, in which some patients experience nuisance in swallowing bulky conventional dosage forms. In order to prevent the dysphagia and enhance patient compliance, orodispersible tablets are introduced as a substitute in oral DDS, designed to disintegrate in mouth without the aid of water [7, 8]. Different methods are adopted to manufacture the orodispersible tablets with the aim of giving fast disintegration to the dosage form as it gets in contact with saliva with good agreeable moth feeling [9]. These orodispersible tablets (ODT) can be administered to any patients having difficulty in swallowing. They are also recognized as mouth dissolvable, melt-in-mouth, fast dissolving, rapi-melts or porous tablets [10].

The main objective of present investigation was to formulate and evaluate fast dissolving oral oral disintegrating tablets of Isosorbide mononitrate with the use of various super disintegrants such as Ac-Di-Sol, Poly Plasdone Xl, and Tulsion 339 for the treatment of angina pectoris.

2. MATERIALS AND METHODS

Isosorbide Mononitrate was procured from RA CHEM Pharma, India. Ac-Di-Sol, Poly Plasdone Xl, Tulsion 339, Sodium saccharin, Talc and Mg. stearate were procured from SD Fine Chemicals Ltd., India.

Preparation of ODT Isosorbide Mononitrate: The Isosorbide mononitrate disintegrating tablets were prepared by direct compression technique. First drug, different concentrations of superdisintegrants (Ac-Di-Sol, poly plasdone Xl and Tulsion339) and required ingredients were weighed accurately then passed through the 40-mesh screen to get uniform size particles and mixed in a glass mortar for 20 min. The obtained blend was lubricated with magnesium stearate and glidant Talc was added and mixing was continued for further 5 min. The blend was evaluated for angle of repose, tab p density, bulk density and compressibility index then the resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine (Lab Press Ltd., India). Compression speed was kept constant for all formulations. Formulation chart for different formulations (F1-F9) was depicted in Table 1. After compression the tablets were evaluated for different parameters.

Table 1: Formulation chart for different formulations (F1-F9)

Ingredients in (mg)	Formulation code								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Isosorbide Mononitrate	20	20	20	20	20	20	20	20	20
Ac-Di-Sol	15	30	45	-	-	-	-	-	-
Poly plasdone Xl	-	-	-	15	30	45	-	-	-
Tulsion339	-	-	-	-	-	-	15	30	45
Sodium saccharin	3	3	3	3	3	3	3	3	3
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
Microcrystalline cellulose 102	72	57	42	72	57	42	72	57	42
Total weight (mg)	120	120	120	120	120	120	120	120	120

Evaluation of tablets [11, 12]

Thickness

The thickness of the tablets was determined by using Digital micrometer. 10 individual tablets from each batch were used and the results averaged.

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation 3 batches were calculated. It passes the test for weight variation test if not more than 2 of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the % shown. It was calculated on an electronic weighing balance.

Friability

The friability values of the tablets were determined using a Roche-friabilator. Accurately weighed six tablets were placed in The Roche friabilator and rotated at 25 RPM for 4 min. Percentage friability was calculated using the following equation.

Friability = ([w_0-w]/w_0) x 100

Where w_0 = weight of tablet at time zero before revolution.

w = weight of the tablet after 100 revolutions

Drug content

The content of drug carried out by 5 randomly selected tablets of each formulation. The 5 tablets were grinded to get powder; this powder was dissolved in pH 6.8 phosphate buffer by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 220nm using UV spectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated.

Disintegration test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 min. and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

Dissolution test

Drug release from Isosorbide Mononitrate tablets was determined by using dissolution test USP type II (paddle). The parameters used for performing the dissolution were pH 6.8 medium as the dissolution medium of quantity 900 ml. The whole study is being carried out at room temperature of 37˚ C and at a speed of 50RPM.5 ml aliquots of dissolution media were withdrawn each time intervals (0, 5, 10,15, 20 and 30 min) and appropriate dilution by UV spectrophotometer at 220 nm. The concentration was calculated using standard calibration curve [13].

Drug-Excipients compatibility studies [14]

Fourier Transform Infrared Spectroscopy (FTIR)

Drug excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions was placed in a vial, and closed with rubber stopper and sealed properly. FTIR studies were performed for pure drug and optimized formulation using Bruker FTIR software. The samples were analyzed between wave numbers 4000 cm^{-1} and 500 cm^{-1}.

Differential scanning colorimetry (DSC)

The possibility of any interaction between the pure drug and the polymer during preparation of tablets was assessed by carrying out thermal analysis of drug and polymer alone as well as physical mixture. DSC analysis was performed using Hitachi DSC 7020. Samples were heated in sealed aluminum pan at a rate of 10 °C/min conducted over a temperature range of 10 to 225 °C under a nitrogen flow of 50 mL/min.

3. RESULTA AND DISCUSSION

Evaluation of pre-compresion parameters of powder blend:

For each formulation blend was prepared and evaluated for various pre compression parameters such as angle of repose, tap density, bulk density, carr's index and hausner ratio. The angles of repose of all blend formulations were found in the range from 25.6±0.65 to 32.3±0.47. The bulk density of all formulations was found in the range of 0.83±0.45 to 0.91±0.25, tapped densiy was in the range of 0.91±0.82 to 0.97±0.91. The carr's index was in the range of 5.21 to 10.31 and finally the hausner ration of prepared blend was in the range from 1.05 to 1.11. The obtained results for all pre-compression parameters of powder blend were found within the range and the results were depicted in Table 2 below.

Table 2: Pre-compression parameters of powder blend

Formulation code	Angle of repose	Bulk density(gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's ratio
F1	31.6±0.75	0.83±0.45	0.92±0.21	9.78	1.11
F2	29.6±0.24	0.87±0.81	0.92±0.58	5.43	1.06
F3	28.2±0.08	0.91±0.25	0.96±0.44	5.21	1.05
F4	30.5±0.11	0.86±0.51	0.91±0.82	5.49	1.06
F5	32.3±0.47	0.87±0.32	0.97±0.91	10.31	1.11
F6	25.6±0.65	0.89±0.47	0.95±0.25	6.32	1.07
F7	30.7±0.39	0.86±0.87	0.93±0.10	7.53	1.08
F8	28.5±0.76	0.87±0.31	0.96±0.53	9.38	1.10
F9	28.4±0.88	0.89±0.22	0.94±0.25	5.32	1.06

Evaluations of post compression parameters of Isosorbide mononitrate ODTs:

All the prepared formulations were evaluated for uniformity of weight using electronic weighing balance and the results were found in the range from 118.35 to 122.02 mg. Hardness of prepared tablets were checked using Monsanto hardness tester and the results were obtained from 3.6 to 5.3 kg/cm^2 the results which was found to be acceptable. Friability was determined to evaluate the strength of the tablets to with stand the abrasion during packing, handling and transporting and the friability results of prepared formulations were showed within the limits. The average percentage friability for all the formulations was between 0.42-0.85%. Prepared tablet formulations were evaluated for drug content, the assay values for all formulations were found to be in the range of 97.40 -99.12%. According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the ODT formulation complies with the standards given in IP. The in vitro disintegration times for prepared formulations were found in the range from 18 – 71 seconds. The results obtained were depicted in Table 3.

Table 3: Evaluation of post compression parameters of Isosorbide Mononitrate ODTs

Formulation codes	Average weight(mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	*In vitro* disintegration Time (sec)
F1	121.42	4.6	0.64	2.6	98.62	25
F2	119.86	3.6	0.80	2.5	97.40	18
F3	118.51	4.8	0.63	2.0	98.72	56
F4	118.35	5.1	0.56	2.3	99.12	34
F5	120.45	4.6	0.79	2.4	97.56	71
F6	122.02	3.9	0.63	2.5	98.14	34
F7	119.44	4.7	0.85	2.8	97.63	28
F8	120.63	5.3	0.42	2.1	97.44	52
F9	118.45	4.3	0.73	2.3	98.65	27

***In-vitro* drug release studies:**

From the in vitro drug release data of all prepared tablet formulations it was evident that the formulations prepared with Ac-Di-Sol powder and Poly plasdone Xl were showed

good drug release in higher concentration of blend i.e. 45 mg. Formulations prepared with Tulsion339 showed maximum drug release i.e., 98.62% (F7 Formulation) at 30 min in 45 mg of blend. Among all formulations F7 formulation considered as optimized formulation which showed maximum drug release at 30 min. i.e. 98.62 %. Tulsion339 were showed good release when compared to other disintegrating agents. The results obtained were depicted in Figure 1.

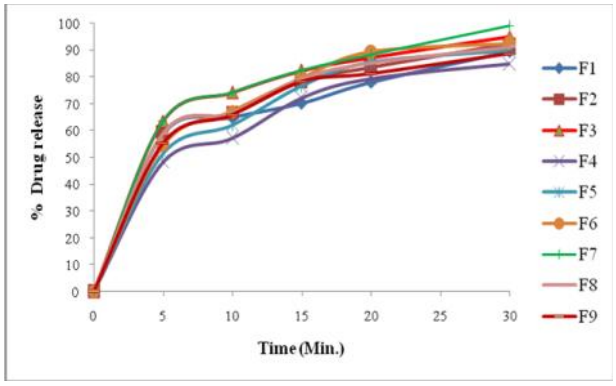

Fig 1: *In vitro* drug release data for F1-F9

FTIR Studies:

Table 4: FTIR spectra for pure drug and optimized formulation (F7)

Characteristic band	Wave Number cm^{-1}	
	Pure drug	Optimized formulation
C-H stretching	2949.81	2921.97
O-H stretching	3322.13	3322.54
C=C stretching	1526.40	1525.45
C-C stretching	1085.61	1085.33

FTIR study was done for pure drug and optimized formulation. From the results FTIR spectra showed that there is no interaction between pure drug and optimized formulation. FTIR spectra results for pure drug and optimized formulation was depicted in Figure 2 and characteristic band and wave numbers were depicted in Table 4.

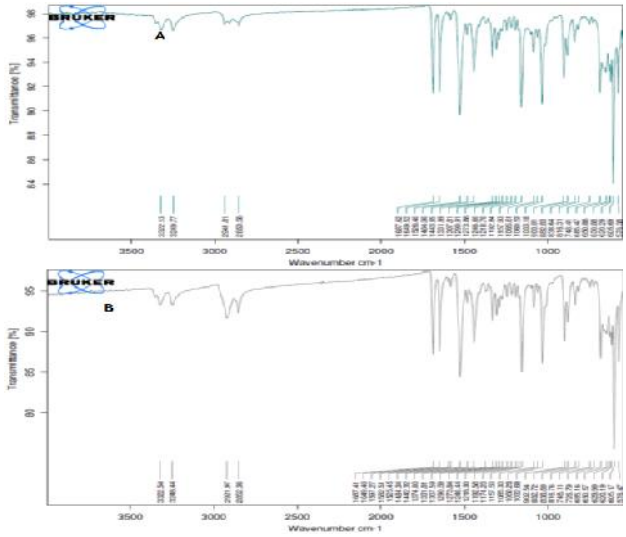

Fig 2: FTIR Spectra for A. Pure drug and B. Optimized formulation

DSC Thermogram:

DSC study was done for pure drug and optimized formulation. DSC thermogram of pure drug and optimized formulation was shown in Figure 3. DSC thermogram of pure drug shows sharp peak at corresponding to its melting point. Isosorbide mononitrate showed a sharp melting endotherm with an onset at 82.41 ºC, peak at 89.65 ºC, and endset at 102.96 ºC. The thermogram of optimized formulation (F7) was showed a typical endothermic peak at 86.68 ºC showing no evidence of incompatibility between the drug and optimized formulation. The DSC thermogram results were showed in Figure 3.

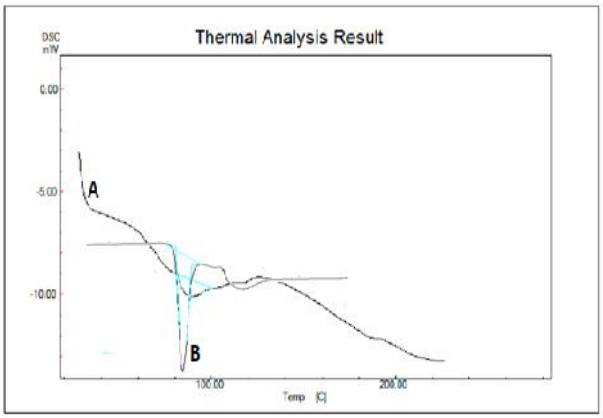

Fig 3: DSC thermogram of A. Pure drug and B. Optimized formulation

4. CONCLUSION

In the present investigation Isosorbide Mononitrate oral disintegrating tablets were prepared by using various super disintegrating agents. From the FTIR and DSC studies it was revealed that there is no major interaction between pure drug and optimized formulation. Before the compression the blend was evaluated for different parameters such as angle of repose, bulk density, tap density and the results were found in with in the I.P. limits. The blend powder showed good flow properties. The prepared tablet formulations were evaluated for thickness, hardness, weight variation, friability, disintegration test and drug release test and the results found within the range, the F7 formulation was showed maximum drug release i.e., 98.62% at 30 min. Hence, from the above results it was concluded that F7 formulation selected as optimized formulation.

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