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Research Article

FORMULATIONS OF ISOSORBIDE MONONITRATE (ISMN) TABLET AND COMPARATIVE STUDY WITH AVAILABLE BRANDS

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ABSTRACT
In the present study new formulations of Isosorbide mononitrate were manufactured by dry granulation method using Talc instead of magnesium stearate and compared with different brands of isosorbide mononitrate tablets available in the market. The present study is divided into two phases. For the first phase new formulation of Isosorbide mononitrate was prepared by dry granulation method and during manufacturing magnesium stearate was replaced by Talc as it is cheaper, less process dependant and requires less blending time as compared to magnesium stearate. Mixing time differences of as little as two minutes can significantly alter the dissolution pattern of finished tablets. In the 2nd phase of present study three different brands of isosorbide dinitrate tablets were randomly selected from the local market using probability sampling tools and evaluated for weight variation test, friability test and hardness test. Disintegration was also conducted according to the methods and guidelines given in BP/USP. The results showed that all parameters like weight-variation, disintegration, hardness, thickness and friability of new formulations are in accordance with the BP/USP limits and the new formulation containing talc showed better potency as compared to other market brands. The most obvious advantage of replacement of magnesium stearate by talc is its better economy, resulting to reduce processing time, less equipment and space required less process validation and lower energy utilization with equal potency and safety.
Keywords: ISMN (Isosorbide mononitrate), SPSS (T-Test), Friability, Disintegration.

INTRODUCTION

Organic nitrates (R-O-NO_2) are oxygen-rich high energy compounds, most commonly used as propellants, explosives and rocket fuels[1]. For more than a century organic nitrates have been prescribed for the treatment of angina, congestive heart failure and acute coronary syndromes[2]. It was determined that they are potential vasodilators which dilate both normal and abnormal coronary arteries by relaxing vascular smooth muscle[3,4]. Experts in the art of tabletting are aware with the basic art of tableting by the three well-known methods, i.e. wet granulation, dry granulation and direct compression[5,6]. Isosorbide-5-mononitrate is used as a vasodilating agent in the management of angina pectoris. By dilatation of the vessels, it lowers the blood pressure and reduces the left ventricular preload and after load and hence produces a reduction of myocardial oxygen requirement. Similar to other nitrites and Isosorbide Mononitrate is converted to nitric oxide (NO), an active intermediate compound which activates the enzyme guanylate cyclase. This stimulates the synthesis of cyclic guanosine 3', 5'-monophosphate (cGMP) which then activates a series of protein kinase-dependent phosphorylations in the smooth muscle cells, and resulting in the dephosphorylation of the myosin light chain of the smooth muscle fiber; resulting in the release of calcium ions results in the relaxation of the smooth muscle cells and vasodilation. Design and formulation of compressed tablet: The most commonly used dosage form for pharmaceutical preparations is the tablet, available in various forms and administered orally. The advantages of this dosage form are manifold: tablets are cost effective to manufacture, easy to dispense and store and convenient for the patient to administer and they provide a various means of delivering the drug. Release of drug from the tablet can be monitored by altering the design and content of the formulation. Since it is a dry dosage form, tablets provide a supportive environment for drug stability and generally have a relatively long shelf life. Tablets are manufactured by applying pressure to a powder, which compresses the powder into a coherent compact. The powder may be consisted of either primary particles or aggregated primary particles (i.e. granules).[7] The dry granulation process is used to form granules without using a liquid solution because the product to be granulated may be sensitive to moisture and heat. Formation of granules without moisture requires compacting and densifying the powders. During this process the primary powder particles are aggregated under high pressure. It involves two main processes either a large tablet (known as a 'slug') is produced in a heavy-duty tableting press (a process known as 'slugging') or the powder is squeezed between two rollers to produce a sheet of material (roller compactor). In every case these intermediate products are broken using a suitable milling technique to produce appropriate granules and which is usually sieved to separate out the desired size fraction. To avoid waste the unused fine material may be reworked. The Dry Granulation method uses mechanical force to densify and compact powders together which forms dry granules. This compaction can be done on a tablet press using "slugging. Another method is used called a Roller Compactor or Chilsonator. This is basically the same kind of machine used to make the charcoal briquettes for our outside grill. The slugged or roller compacted powders are then milled, final blended and compressed on a tablet press (98 % unique cotent).

MATERIALS AND METHODS:

Manufacturing of new formulations

Check all raw materials on weighing order that are to be used in the manufacturing procedure for name, quantity, code number and appearance of material at the time of use in manufacture. Following steps are involved:

- Transfer all ingredients into suitable polyethylene bag and mix for 15 minutes. If lumps are present, sieve it through mesh no.16.
- Take out granules in suitable labeled container lined with polyethylene bag.
- Adjust compression machine with die and punches.

❖ Set and clean the machine.
❖ Start compression of the tablets according to specifications.
❖ Perform in-process QC (quality control) tests periodically and record on standard compression control sheet.
❖ After completion of compression, collect compressed tablets in properly cleaned polyethylene lined labeled container. (100 % unique)

Comparative Analysis

All parameters (wt. variation, thickness, hardness, disintegration, dissolution) of new formulations were carried out and results showed that they are in accordance with BP/USP limits. In the 2nd phase of present study three different brands of Isosorbide mononitrate tablets were randomly selected from the local market using probability sampling tools and evaluated for weight variation, hardness, friability, disintegration, dissolution (by using HPLC) and pharmaceutical assay (by using spectrophotometer) were conducted according to the methods and guidelines given in BP/USP. Every above mentioned test was performed in strict compliance of Good Laboratory Practices (GLP). Although there are several procedures which apply specifically to tablets and which are designed in the main to assure that the patient receives a product containing the required amount of drug substance in a form which enables the later to exert its full pharmacological response.[8,9]

Weight variation test

Weight variation test of above mentioned tablets proved strictly that all the tablets were in accordance to the BP/USP requirements that not more than two tablets out of 20 tablets should cross ± 7.5 % deviation. Similarly their statistical control chart (shewart chart) shows that all the market brands and new formulations of isosorbide mononitrate tablets were in range of the upper and lower limits.

Thickness test

Thickness of all tablets and new formulations including average, standard deviation, upper and lower limits are in accordance with BP/USP.

Hardness test

In the heady days of fundamental empiricism, cracking the compressed tablets b/w the finger and thumb and bouncing them on the production area floor was considered sufficient control. Since harness is strain rate dependent and dictated, by the operator, the results can be variable, depending on how quickly the load is applied. Hardness measurement provides production control over friability, disintegration and dissolution. The resistance of the tablet to chipping, abrasion or breakage during storage, transportation and handling before usage depends on its hardness. Hardness test of different brands and new formulations of isosorbide mononitrate tablets was found to be in conjunction with the stated guidelines as given in BP/USP. Similarly the official limit of hardness stated in BP/USP is not less than 4.00 Kg of pressure is required to break a tablet, and all of the samples were in accordance with the limit.

Friability test

This test is intended to observe, under defined condition the friability of uncoated tablets, the phenomenon where by tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. Friability of all tablets was less than 1 %. Therefore it is also compliance with the BP/USP standards.

Disintegration test

The following factors can affect disintegration time of a tablet. Type of granulating agent

- The diluents used.
- The use of water repellent lubricant.
- The type and quantity of disintegrating agent.
- The force used to compress the tablet.

Disintegration test was conducted on all brands and new formulations of isosorbide mononitrate tablets. The official range in BP/USP for uncoated tablets is not more than 15 minutes. Results showed that all tablets were in accordance to BP/USP. (96 % unique)

RESULTS

Weight variation test of the above mentioned tablets proved statistically that all the tablets were in accordance to the BP/USP requirements (Table 2 and 3). Thickness of all tablets and new formulation showing average, standard deviation, upper and lower limits are in accordance with BP/USP (Table 4 and 5). Hardness of different brands and new formulation was found to be in conjunction with the stated guidelines as given in BP/USP (Table 6 and 7). Friability of all tablets was less than 1 %. Therefore it is also compliance with the BP/USP standards. Its data is given in (Table 8). Disintegration test was conducted on new formulation and all brands. The official limit in BP/USP for uncoated tablets is not more than 15 minutes. Results showed that every tablet was in accordance to BP/USP (Table 9).

DISCUSSION

In the present study new formulation of isosorbide mononitrate was manufactured and compared with available market brand of isosorbide mononitrate tablets. For manufacturing of new formulations dry granulation method was used. Dry granulation has the advantage over direct compression in that once the slugs are formed, no segregation of drug and excipient can occur. In addition the method is useful for hydrolysable and thermolabile drugs. All parameters of (wt. variation, disintegration, thickness and hardness of new formulation were carried out and results showed that they are in accordance with the BP/USP limits. The results indicate that the new formulations have better results as compare to market brand. After applying SPSS we conclude results of weight, hardness, thickness friability and disintegration test that shows highly significant results in each case. For weight variation t –test value of new formulation and available brand is 827, df = 5 with p- value 0.000. For thickness t value = 466, hardness 512, friability 45 and disintegration values 55 with degree of freedom df = 5 and p values = 0.00 > 0.005 in each case. These values indicate that new formulation is better than available brand Table 10.

Table 1: Specification of drugs with batch no

S. No.	Product name	Assigned no.	Code no.	Batch no.
01	Monis	ISMN-1	1624	B322
02	New Formulation	ISMN-NEW	110	T-2

Table 2: Statistical Weight Variations

S. No.	Code no.	Batch no.	Average (g)	Standard deviation	Upper limit (X + 3S)	Lower limit (X - 3S)
ISMN-1	1624	B322	0.1716	0.000706	0.173643	0.169507
ISMN-NEW	110	T-2	0.1415	0.000986	0.144458	0.138542

Table 3: Weight Variation Test

S. No.	Code no.	Batch no.	Result (g)	BP/USP Specification	Deviation from BP/USP Specification
ISMN-1	1624	B322	0.1716	Deviation should be ± 7.5 %	Within specified limit
ISMN-NEW	110	T-2	0.1415		Within specified limit

Table 4: Statistical Thickness

S. No.	Code no.	Batch no.	Result (mm)	Standard deviation	Upper limit (X + 3S)	Lower limit (X - 3S)
ISMN-1	1624	B322	3.745	0.036893	3.855679	3.634321
ISMN-NEW	110	T-2	3.485	0.133437	3.885311	3.084689

Table 5: Thickness Test

S. No.	Code no.	Batch no.	Thickness (mm)	BP/USP Specification
ISMN-1	1624	B322	3.745	No BP/USP Specification
ISMN-NEW	110	T-2	3.485	No BP/USP Specification

Table 6: Statistical Hardness

S. No.	Code no.	Batch no.	Average (Kg)	Standard deviation	Upper limit (X + 3S)	Lower limit (X - 3S)
ISMN-1	1624	B322	4.3	0.760482	6.581446	2.018554
ISMN-NEW	110	T-2	7.71	0.467143	9.9111429	6.308571

Table 7: Hardness test

S. No.	Code no.	Batch no.	Result (Kg)	BP/USP Specification	Deviation from BP/USP Specification
ISMN-1	1624	B322	4.3	Not less than 4.00 kg	Within specified limit
ISMN-NEW	110	T-2	7.71		Within specified limit

Table 8: Friability Test

S. No	Code no.	Batch no.	Result (%)	BP/USP Specification	Deviation from BP/USP Specification
ISMN-1	1624	B322	0.23	Not more than1%	Within specified limit
ISMN-NEW	110	T-2	0.14		Within specified limit

Table 9: Disintegration Test

S. No	Code no.	Batch no.	Disintegration time (min : sec)	BP/USP Specification	Deviation from BP/USP Specification
ISMN-1	1624	B322	3 minutes	Not more than 15 minutes	Within specified limit
ISMN-NEW	110	T-2	3 minutes and 25 sec		Within specified limit

Table 10: Paired sample T -Test of new formulation with market brand

Paired Differences		T -Test					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95 % Confidence Interval of the Difference				
					Lower	Upper			
Weight	ism- ismn	.03020	.0000	.00004	.03011	.0302	827.06	5	.000
Thickness	ism - ismn	.26033	.0013	.00056	.25890	.26177	466.73	5	.000
Hardness	ism - ismn	3.41333	.0163	.00667	-3.430	-3.396	512.00	5	.000
Friability	ism - ismn	.09450	.0050	.00206	.08920	.09980	45.839	5	.000
disintegration	ism - ismn	25.000	1.095	.44721	-26.100	-23.80	-55.902	5	.000

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