Manufacturing of new formulations of Isosorbide dinitrate by direct compression method and their comparative evaluation with different brands available in the market.

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Abstract:

The aim of this study was to develop new formulations of Isosorbide dinitrate by direct compression method using Talc instead of magnesium stearate. The present study is divided into two phases. In the first phase new formulation of Isosorbide dinitrate was prepared by direct compression 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. Blending time differences of as little as two minutes can significantly alter the dissolution pattern of finished tablets. In the 2nd phase three different brands of isosorbide dinitrate tablets were randomly selected from the local market using probability sampling tools and evaluated for weight variation, hardness, friability, disintegration, dissolution (by using HPLC). Pharmaceutical assays (by using spectrophotometer and HPLCr) were also conducted according to the methods and guidelines given in BP/USP. The results showed that all parameters (weight-variation, thickness, hardness, friability, disintegration, dissolution and Pharmaceutical assays 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, owing to reduce processing time, less equipment and space required less process validation and lower energy utilization with equal potency and safety.

Key words: ISDN (Isosorbide dinitrate), Talc, Mg-Stearate, Friability, Disintegration, Dissolution, Pharmaceutical Assay.

Introduction:

Organic nitrates (R-O-NO2) are oxygen-rich high energy compounds, used widely as propellants, explosives and rocket fuels [1,2]. For more than a century organic nitrates have been prescribed for the treatment of stable angina, acute coronary syndromes and congestive heart failure [3]. It was determined that they are potential vasodilators which dilate both normal and abnormal coronary arteries by relaxing vascular smooth muscle [4-6]. Experts in the art of tableting are awared with the basic art of tableting by the three well-known methods, i.e. wet granulation, roller compaction and direct compression [7-9]. Current usage of the term "direct compression" is used to define the process by which tablets are compressed directly from the powder blends of active ingredients and suitable excipients. No pre-treatment of the powder blends by wet or dry granulation is involved [10]. It has been estimated that less than 20 percent of pharmaceutical materials can be compressed directly into tablets [11].

Isosorbide dinitrate (ISDN) is 1,4:3,6-dianhydro-D-glucitol 2,5-dinitrate, an organic nitrate with molecular wt =236.1[12].

Exact mechanism of actions of Isosorbide dinitrate is remain unclear but it would appear to act in a similar fasion , as has glyceryl trinitrate. ISDN liberated nitric oxide (NO) activates guanylate cyclase which increases the synthesis of cyclic GMP[13]. It is possible that NO combines with sulfahydryl groups in the endothelium and produces S-nitrosothiols that stimulate guanylate cyclase production. This is enhanced by N-acetyl cysteine, which provides a source of sulfhydryl groups. How cyclic GMP produces vascular relaxation is not exactly known but it does reduce stored calcium and thus interferes with calcium- activated smooth muscle contraction [14].

Design and formulation of compressed tablet**:** The most commonly used dosage form for pharmaceutical preparations is currently the tablet, available in various forms and administered orally. The advantages of this dosage form are manifold: tablets are cost effective to manufacture, convenient to dispense and store, and easy for the patient to administer, and they provide a versatile means of delivering the drug. Release of drug from the tablet can be controlled by altering the design and content of the formulation. Also, since this 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 bed, which compresses the powder into a coherent

compact. The powder may consist of either primary particles or aggregated primary particles (i.e. granules).Compressed tablets are formed by compression and in their simplest form, contain no special coating. They are made from powdered, crystalline or granular materials alone or in combination with binders, disintegrants, controlled release polymers, lubricants, diluents and in many cases colorants. The vast majority of tablets commercialized today are compressed tablets either in an uncoated or coated state.Direct compression consists of compressing tablets directly from powdered material without modifying physical nature of the material itself [15].

The term "direct compression" is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required.An ideal direct compression excipient should possess the following attributes:

i) It should have good compressibility.
ii) It should possess good hardness after compression, that is material should not possess any deformational properties; otherwise this may lead to capping and lamination of tablets.
iii) It should have good flowability.
iv) It should be physiologically inert.
v) It should be compatible with wide range of API.
vi) It should be stable to various environmental conditions (air, moisture, heat, etc.).
vii) It should not show any physical or chemical change in its properties on aging.
viii) It should have high dilution potential. i.e. Able to incorporate high amount of API.
ix) It should be colourless, odorless and tasteless.
x) It should accept colourants uniformity.
xi) It should possess suitable organoleptic properties according to formulation type, that is in case of chewable tablet diluent should have suitable taste and flavor. For example mannitol produces cooling sensation in mouth and also sweet test.
xii) It should not interfere with bioavailability and biological activity of active ingredients.
xiii) It should be easily available and economical in cost.

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:

1. Transfer all ingredients into suitable polyethylene bag and mix for 15 minutes. If lumps are present, sieve it through mesh no.16.
2. Take out granules in suitable labeled container lined with polyethylene bag.
   - Adjust compression machine with die and punches.
   - Set and clean the machine.
   - Compress the tablets according to specifications.
   - Perform in-process quality control tests periodically and record on standard compression control sheet.
   - When compression is completed, store compressed tablets in properly cleaned polyethylene lined labeled container.

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 this study three different brands of Isosorbide dinitrate 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.

All the above mentioned tests were carried out in strict compliance of Good Laboratory Practices (GLP).However there are a number of 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 action.

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 dinitrate 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 tablets b/w the finger and thumb and bouncing them on the production area floor was considered sufficient control[16]. Hardness test of different brands and new formulations of isosorbide dinitrate tablets was found to be in conjunction with the stated guidelines as given in BP/USP. Similarly the official range of hardness stated in BP/USP is not less than 4.00 Kg of pressure is required to break a tablet, so all of the samples were in accordance with the limit.

Friability test:

This test is intended to determine, 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.(British Pharmacopoeia 2000)

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 amount of disintegrating agent.
- The force used to compress the tablet.

Disintegration test was conducted on all brands and new formulations of isosorbide dinitrate tablets. The official range in BP/USP for uncoated tablets is not more than 15 mins. Results showed that all tablets were in accordance to BP/USP.

Dissolution test:

This test is used to determine the dissolution rate of the active ingredient of solid dosage form. Suitable dissolution characteristic is an important property of a satisfactory tablet [17].The in vitro dissolution of one standard (6 samples) and three brands (18 samples) and one new formulation (6 samples) of isosorbide dinitrate tablets was performed by using HPLC. All samples were in accordance to the specified limits as given in BP/USP.

Pharmaceutical assay:

The assays described are the official methods upon which the standard of the pharmacopoeial depend. By using spectrophotometer assay was carried out on all brands and new formulation of isosorbide dinitrate tablets during the study. All tablets have potencies in accordance of required specification.

Results:

Weight variation test:

Wt. variation test of the above mentioned tablets proved statistically that all the tablets were in accordance to the BP/USP requirements (Table-2&3).

Thickness test:

Thickness of all tablets and new formulation including average, standard deviation, upper & lower limits are in accordance with BP/USP(Table-4&5)

Hardness test:

Hardness test of different brands &new formulation was found to be in conjunction with the stated guidelines as given in BP/USP (Table-6&7).

Friabilty test:

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

It was conducted on all brands & new formulation. 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 (Table-9)

Dissolution test:

The invitro dissolution of three brands(18 samples) and one new formulation(6 samples)of isosorbide dinitrate tablets was performed by using HPLC. All samples are in accordance to the specified limits as given in BP/USP (Table-10).

Pharmaceutical assay: By using spectrophotometer assay was carried out on all brands and new formulation of isosorbide dinitrate tablets during the study. All tablets have potencies in accordance of required specification (Table-11).

Table 1:

S.no	Product name	Assigned no.	Code no.	Batch no..
01	ISDIN	ISDN-1	18853	B 61
02	ISOBID	ISDN-2	17405	7J 254
03	ISORDIL	ISDN-3	95542	O2B0257
04	NEW FORMULATION	ISDN-NEW	786	T-2

Table II: Statistical weight variations

S.no.	Code no.	Batch no.	Average (Gm)	Standard deviation	Upper limit (X+3S)	Lower limit (X-3S)
ISDN-1	18853	B61	0.1759	0.002658	0.183904	0.167956
ISDN-2	17405	7J254	0.1312	0.002177	0.137786	0.124724
ISDN-3	95542	02B0257	0.1761	0.005606	0.192928	0.159292
ISDN-NEW	786	T-2	0.1756	0.000723	0.177769	0.173431

Table III: Weight variation test

S.no.	Code no.	Batch no.	Result (Gm)	BP/USP Specification	Deviation from BP/USP Specification
ISDN-1	18853	B 61	0.1759	Deviation should be ±7.5%	Within specified limit
ISDN-2	17405	7J254	0.1312		Within specified limit
ISDN-3	95542	02B0257	0.1761		Within specified limit
ISDN-NEW	786	T-2	0.1756		Within specified limit

Table IV: Statistical thickness

S.no.	Code no.	Batch no.	Result (mm)	Standard deviation	Upper limit (X+3S)	Lower limit (X-3S)
ISDN-1	18853	B61	3.85	0.057735	4.023205	3.676795
ISDN-2	17405	7J254	2.565	0.102875	2.873625	2.256375
ISDN-3	95542	02B0257	3.3	0.084984	3.554952	3,045048
ISDN-NEW	786	T-2	3.7	0.145297	4.135891	3.264109

Table V: Thickness test

S.no.	Code no.	Batch no.	Thickness (mm)	BP/USP SPECIFICATION
ISDN-1	18853	B 61	3.85	No BP/USP Specifications
ISDN-2	17405	7J254	2.565	NoBP/USP Specifications
ISDN-3	95542	02B0257	3.3	No BP/USP Specifications
ISDN-NEW	786	T-2	3.7	No BP/USP Specifications

Table VI: Statistical hardness

S.no.	Code no.	Batch no.	Average (Kg)	Standard deviation	Upper limit (X+3S)	Lower limit (X-3S)
ISDN-1	18853	B61	6.185	1.136772	9.595316	2.774684
ISDN-2	17405	7J254	5.02	0.720031	7.180093	2.859907
ISDN-3	95542	02B0257	4.59	0.485226	6.045678	3.134322
ISDN-NEW	786	T-2	7.28	0.656675	9.250025	5.309975

Table VII: Hardness test

S.no.	Code no.	Batch no.	Result (Kg)	BP/USP Specification	Deviation from BP/USP Specification
ISDN-1	18853	B 61	6.185	Not less than 4.00 KG	Within specified limit
ISDN-2	17405	7J254	5.02		Within specified limit
ISDN-3	95542	02B0257	4.59		Within specified limit
ISDN-NEW	786	T-2	7.28		Within specified limit

Table VIII: friability test

S.no	Code no.	Batch no.	Result (%)	BP/USP Specification	Deviation from BP/USP Specification
ISDN-1	18853	B 61	0.23	Not more than1%	Within specified limit
ISDN-2	17405	7J254	0.35		Within specified limit
ISDN-3	95542	02B0257	0.14		Within specified limit
ISDN-NEW	786	T-2	0.12		Within specified limit

Table IX: Disintegration test

S.no	Code no.	Batch no.	Disintegration time (min:sec)	BP/USP Specification	Deviation from BP/USP Specification

ISDN-1	18853	B 61	3min:30sec	Not more than 15min	Within specified limit
ISDN-2	17405	7J254	1min:27sec		Within specified limit
ISDN-3	95542	02B0257	0 min:12sec		Within specified limit
ISDN-NEW	786	T-2	1min:45sec		Within specified limit

Table X: Dissolution test (using hplc)

S.no	Code no.	Batch no.	Results (%)	BP/USP Specification	Deviation from BP/USP Specification
ISDN-1	18853	B 61	104.38%	Not less than 75%	Within the specified limit
ISDN-2	17405	7J254	106.19%		Within the specified limit
ISDN-3	95542	02B0257	88.90%		Within the specified limit
ISDN-NEW	786	T-2	110.33%		Within the specified limit

Table X1: Pharmaceutical assay

S.no	Code no.	Batch no.	Potency (%)	BP/USP Specification	Deviation from BP/USP Specification
ISDN-1	18853	B 61	98.82%	Between 90%to110%	Within specified limit
ISDN-2	17405	7J254	109.65%		Within specified limit
ISDN-3	95542	02B0257	102.21%		Within specified limit
ISDN-NEW	786	T-2	104.14%		Within specified limit

Discussion:

In the present study new formulations of isosorbide dinitrate were manufactured and compared with different brands of isosorbide dinitrate tablets available in the market. For manufacturing of new formulations direct compression method was used. Regardless of the granulation method, the comparative simplicity of the direct compression process offers obvious advantages, such as

1. Economy
2. Elimination of heat and moisture
3. Optimization of tablet disintegration
4. Stability

Although there are many significant advantages of direct compression over granulation, there also are important limitations;

1. Uniform blending and prevention of unblending of low-dose drugs.
2. Fillers often are costlier than fillers used in granulation.
3. Physical properties and functional specifications are more sritical; properties of raw materials must be defined and carefully controlled.
4. Limitations in producing colored tablets.
5. Dust problems.
6. Limitations in the dilution capacity of filler –binder.
7. More sensitive to lubricant softening and over mixing than granulations.

The design of the formulation and selection of excipients is especially critical in tablet dosage forms. Excipients function to provide compatibility, lubrication, flow properties, disintegration efficiency, and wetting etc. Poor choice of excipients may give rise to poor characteristics which can be important in packaging, storage and patient acceptance. During manufacturing of ISDN-NEW, magnesium stearate was replaced by talc as it is cheeper to magnesium stearate. 2nd important thing is that the problems with Mg-stearate are highly process

dependent. For example, blending time differences of as little as two minutes can significantly alter the dissolution pattern of finished tablets.All parameters (wt.variation, thickness, hardness & disintegration) of new formulations were carried out & results showed that they are in accordance with the BP/USP limits. The results indicate that the new formulations have better dissolution as compared to dissolves more quickly than Mg-stearate. Their assay shows that their potency also better than other market brands.

Conclusion:

The most obvious advantage of direct compression method is it's greater economy, owing to reduce processing time, less equipment and space required, less process validation and lower energy utilization generally only blending and compression are required. In the manufacturing of new formulations of isosorbide dinitrate magnesium stearate was replaced by talc as it cheeper and comparative evaluation of new formulation with different brands shows that new formulation has better result of assay as compared to market brands.

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