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RESEARCH ARTICLE

Study and Impact Evaluation of Particle Size Distribution on Physicochemical Properties of Three Different Tablet Formulations through Sieve Technology

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ABSTRACT

The objective of this study was to evaluate the impact of Particle size distribution by means of sieving of granules for tablet compression through mesh screen and the relationship between this size distribution and physical & chemical properties of tablets (e.g., hardness, thickness, target weight, appearance, friability, disintegration time, dissolution and potency). Optimization of particle size distribution was also carried out for taking the effects of hardness, thickness, target weight, appearance, friability, disintegration time, dissolution and potency into consideration. The physical properties of granules for tablet compression and tablets were found to be significantly affected by this factor. That was mean, the different particle size distribution with different size of mesh screen found to be governed the physical and chemical properties of tablets. So, it can be said that the evaluation parameters such as hardness, thickness, target weight, appearance, friability, disintegration time, dissolution and potency was found to be affected by the particle size distribution. Potency was not affected significantly due to different particle size distribution. Dissolution rate increased with decreasing granule size (over the range 16-20 mesh to 60-80 mesh) and probability of rising sticking problem &poor flow property was observed with decreasing granule size but not strictly proportionally to the corresponding increase in the apparent surface area of the granules. Increasing starch content of granules (varied from 0 to 20 per cent) resulted in an increase in dissolution rate. Increasing precompression pressure (varied from 715 to 5720 Kg/cm^2) caused an increase in dissolution rate. This was probably due to fracturing of the harder granules into smaller particles with greater specific surface area or bonding of the softer granules (prepared at lower slugging pressure) during their compression into tablets.

KEYWORDS

INN, Mesh, Particle Size Distribution, Surface Area and Physico-Chemical Property

INTRODUCTION

Mesh size is material is often used in determining the particle size distribution of a material. Mesh size is the number of openings per (linear) inch of mesh.

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To calculate the size of the openings in a mesh the thickness of the wires making up the mesh material have taken into account. Mesh size given as 4*4 means the number of squares in one inch horizontally is 4 and vertically is 4.Some standards use the mesh designation as the number of wires rather than the size of openings. There can be significant differences in particle size passing small laboratory screens

versus large heavy-duty industrial screens due to the different wire sizes used. Thicker wire results in a smaller opening size for an equivalent mesh.

Sieves for pharmaceutical testing are constructed from wire cloth with square meshes, woven from wire of brass, bronze, stainless steel or any suitable materials. Sieves shouldn't be coated or plated. There must be no reaction between the material of the sieve and the substance to be sieved (Subrahmanyam C.V.S. et al. 2001). The primary considerations for sieves are given to the size and shape of aperture opening. Square meshes are arranged as per the specifications. Sieves commonly used in pharmaceutical processing include Woven wire sieves, bolting cloth sieves, closely spaced bars (screens), Punched plates. There are some Common standards used for sieves which include-Tyler standard sieves series (in USA), US standard sieve series (in USA), and British standard sieve series (in UK). German DIN (Deutsche Industrienormein) (in Germany and Europe), IP standard sieve series (in India), International test sieve series (ISO) (in worldwide). An ideal screen would sharply separate the feed mixture in such a way that the smaller particle in the oversize would be just larger than the largest particle in the undersize.

Sieving is the most widely used method for measuring particle size distribution because it is inexpensive, simple and rapid with little variation with operators. A sieve consists of a pan with a bottom of wire cloth with square openings. In the USA, two standards of sieves are used. In the Tyler Standard Scale, the ratio of the width of openings in successive sieves is √2. The Tyler Standard Scale is based on the size of opening (0.0029µ) in a wire cloth having 200 openings per linear inch, i.e., 200-mesh. The USA standard scale proposed by the National Bureau of Students in general uses the ratio √2, but it is based on opening of 1mm (18-mesh)

The procedure involves the mechanical shaking of a simple through a series of successively smaller sieves, and the weighing of the portion of the sample retained on each sieve. The type of motion influences sieving: vibratory motion is most efficient, followed successively by side-tap motion, bottom-up motion, rotary motion with tap, and rotary motion. Time is an important factor in sieving. The load or thickness of powder per unit area of sieve influences the time of sieving; for a given set of sieves, the time required to sieve a given material is roughly proportional to the load placed on the sieve. Therefore, in size analysis by means of sieves, the type of motion, time of sieving, and the load should be standardized. The size assigned to the sample retained is arbitrary, but by convention, the size of particle retained is taken as the arithmetic or geometric mean of the two sieves (a powder passing a 30-mesh and retained on a 45-mesh sieve is assigned an arithmetic mean diameter of (590+350)/2 or 470 microns). (Lachman et al., 1987) and (Marderosian., 1990)

Screening is a method of separating particles according to size alone. The basic technique involved is passing the particles through a series of sieves of uniform size. In this, the particles drop through the openings due to gravity. Coarse particles can drop easily through large openings, but it is difficult to screen fine powders. The process can be hastened by including some type (mode) of motion (movement) to the particles. Size separation is basically assisted by three methods. Such as agitation, brushing and Centrifugal force

Sizing is a unit operation that involves the separation of a mixture of various sizes of particles into two or more portions by means of screening surfaces. Sizing is also known as sieving, sifting, classifying or screening. Size separation, Size reduction. This technique is based on the physical differences between the particles such as size, shape, and density. Particles can be separated into individual sizes using sieves. The final portion consists of more uniform size. The material that remains in the given screening surface is known as oversize or plus material. The material passing through the screening surface is known as undersize or minus material. (Subrahmanyam C.V.S. et al.

2001). There are a few official definitions or terms describing the degree of chemical substance.

Coarse (No. 20 powder) means100% pass through a no. of 20 size sieve; not more than 60% may pass through a No. 40 sieve and Moderately Coarse (No. 40 powder) which denotes that 100% pass through a no. 40 sieve: not more than 60% may pass through a no. 60 sieve as well as Fine (No. 80 powder) 100% pass through a no, 80 sieves. Finally, Very fine: (No. 120 powder) means 100% pass t rough a no. 120 sieve and he sub sieve range, which has been defined to include particle size from none micron to a somewhat arbitrary 50 micron or more, requires more sophisticated means of particle size analysis.(Dittert.1974)

Powders and granular materials are sometimes described as having a certain mesh size (e.g. 30 mesh sand).More precise specifications will indicate that a material will pass through some specific mesh (that is, have a maximum size; larger pieces won't fit through this mesh) but will be retained by some specific tighter mesh (that is, a minimum size; pieces smaller than this will have passed through the mesh). This type of description establishes a range of particle sizes.

One notation for indicating particle size distribution using mesh size is to use + and - designations. A "+" before the sieve mesh indicates the particles are retained by the sieve, while a "-" before the sieve mesh indicates the particles pass through the sieve. This means that typically 90% or more of the particles will have mesh sizes between the two values. For instance, if the particle size of a material is described as -80/+170 (or could also be written -80 +170), then 90% or more of the material will pass through an 80 mesh sieve and be retained by a 170 mesh sieve. Using the conversion chart below, the resulting particles will have a range of diameters between 0.089 and 0.178 mm (89 and 178 micrometers).(Marderosian., 1990)

The compressed tablet is by far the most widely used dosage form, having advantages for both producer and user. The tablet is the most popular dosage form because it provides advantages for all concerned in the production and consumption of medicinal products. From the viewpoint of the pharmacist, tablets are easy to dispense, while the patient receives a concentrated and readily transportable and consumed dosage form. Furthermore, if properly prepared, tablets provide a uniformity of dosage greater than that of most other medicines, and appropriate coating can mask unpleasant tastes and improve patient acceptance.

The tablet also provides a versatile drug delivery system. Though most tablets are intended to be swallowed intact, the same basic manufacturing process, associated with appropriate formulation, provides medicines for sublingual, buccal, rectal, and vaginal administration, together with lozenges, soluble, dispersible, and effervescent tablets. In addition, techniques that can delay or otherwise modify the release of the active ingredient from the tablet are available. The goal of table manufacturing technology is to provide a smooth production of drug & provide a therapeutic amount of drug to achieve a desired therapeutic action.

There are many factors involved in table formulation technology. One of prominent factors is mesh size determination which affect various formulation. In tableting technology mesh size is one of the important factors because it determines the particle size of granules or powder for the compression or other processing. Finally particle size determines the physical & chemical properties of formulation (Terence, A., 1975.) Tablet specifications are very tight & list of possible defect is long. But this research focuses on variation in tablet appearance, dissolution & assay. It pinpoints the possible causes of these defects and offers an advice on preventing & fixing the source of the problems. The variation often stems from changes in the properties of the raw materials-active ingredient – from batch to batch. Naturally, the goal is to minimize these. Optimum particle size distribution for making the perfect tablet is very much tough.

A particle size distribution within the right range produces a good looking tablet, but the nature of distribution depends on the tablet size.

MATERIALS AND METHOD

In order to study the effect of mesh screen used to sieve the granules of tablet to evaluate their physico-chemical property, following materials and method applied as per table no. 3.1 and 3.2.

Table 3.1: Used equipment for preparing tablets of formulations (F1 to F3)

Name of equipment	Source
Vibratory Sifter with SS screen	Gansons,mumbai, India
Planetary Mixer	Gansons,mumbai,India
Multimill	India
Oil jacketed vessel	Mohakhali,Bangladesh.
Fluid Bed Dryer (Sapphire)	Mumbai, India
Cad Mill	Ahmedabad, India
Double Cone blender	Shang yuh, Taiwan
compression machine	Manesty, England
Tablet Polishing Machine	Taiwan
Vibratory Sifter	Gansons,mumbai, India
Planetary Mixer	Gansons,mumbai,India
Silverson Stirrer	Silverson machineries Ltd. England
Drum Blender	Mohakhali, Bangladesh
2nd Compression Machine	Clit, India
Fitz Mill/Cad Mill/ Apex Mill	Ahmedabad, India
Sartorius Electronic Balance	Germany
Pharmatest friability tester	Germany
Erweka Hardness and Thickness tester	Germany
Pharmatest Disintegration machine	Germany
Erweka dissolutiontester	Germany

Preparation of Tablet of Formulation F1 (Experiment-1, 2 & 3)

In Case of Using 22 Sieving Mesh SS Screen

The tablet was prepared by wet granulation. During wet granulation povidone is mixed with water then mixed with gradually Etoricoxib, microcrystalline Cellulose, Starch 1500 (Pregelatinised), lactose. Before lubrication pre-screen the dried granules through 22 mesh SS screen fitted with vibratory sifter and crush the oversized granules by using fitted with 0.065" (1.65 mm)SS Screen and again pass the crushed granules through 22 mesh. Then blend the available dried granules by using Sodium Starch Glycolate, purified talc, magnesium Stearate. Then compressed the available granules by using 16 station compression machine.

In Case of Using 30 Sieving Mesh SS Screen

Process as above mentioned way but before lubrication dried granules was pre-screen the dried granules through 30 mesh SS screen fitted with vibratory sifter and crush the oversized granules by using fitted with 0.065" (1.65 mm) SS Screen and again pass the crushed granules through 30 mesh SS screen and followed as above mentioned process or then blend the available dried granules by using Sodium Starch Glycolate, purified talc, magnesium Stearate. Then compressed the available granules by using 16 station compression machines.

In Case of Using 40 Sieving Mesh SS Screen

Process as above mentioned way of sieving through 22 mesh but before lubrication dried granules was pre-screen the dried granules through 40 mesh SS screen fitted with vibratory sifter and crush the oversized granules by using fitted with 0.065" (1.65 mm) SS Screen and again pass the crushed granules through 40 mesh SS screen and followed as above mentioned process or then blend the available

Table 3.2: Materials used to prepare tablet in three different formulations

Formulation	Name of Ingredient	Quantity/ Tablet (mg)	Source of materials
F1	Etoricoxib	90.00	Cadila Health care Ltd. India
	Lactose	31.05	DMV fontera excipient ltd. Newzeland
	Microcrystalline Cellulose	27.00	Minthai chemical corporation, Taiwan.
	Starch 1500	14.40	Colorcon, USA
	Kollidon 30*	5.40	ISP technologies Inc. UK
	Sodium Starch Glycolate	7.20	Young Zip, Taiwan.
	Talc	3.60	Asian Mineral resource Co. Ltd Thailand.
	Magnesium Stearate	1.35	Dr. Paul Lohman, Germany
Total		**180.00**	
F2	Azithromycin Dihydrate	556.760	Alembic ltd. India.
	Maize Starch	21.000	Cargill Deuschland GmbH
	Povidone (K-90)	9.667	ISP technologies Inc, USA
	Crospovidone (KollidonCL)	10.000	ISP sales UK Ltd.
	Colloidal Silicon Dioxide	6.513	Cabot sammar Ltd. India
	Sodium Starch Glycolate	13.220	Yung zip chemical Ltd. Taiwan
	Magnesium Stearate	4.000	Dr. Paul Lohman, Germany
	Talc	6.553	Asian Mineral resource Co. Ltd Thailand
	Spectracol Quinoline Yellow LK	0.220	Sesient colors UK Ltd.
	Microcrystalline Cellulose	32.067	Minthai chemical corporation, Taiwan.
Total		**660.000**	
F3	Triamterene	50.000	Moehs catalana SL, Spain
	Hydrochlorothiazide	25.000	Ipca laboratories Ltd, Spain
	Lactose	5.5625	DMV fontera excipient ltd. Newzeland
	Maize Starch	50.000	Cargill Deuschland GmbH
	Maize Starch (For Paste)	57.500	Cargill Deuschland GmbH
	Microcrystalline Cellulose	12.000	Minthai chemical corporation, Taiwan.
	Starch 1500 (Pregelatinised)	40.000	Colorcon, USA
	Sodium LaurylSulphate	16.500	NJC Corporation, Taiwan
	Sodium Starch Glycolate	1.300	Yung zip chemical Ltd. Taiwan
	Talc	16.500	Asian Mineral resource Co. Ltd Thailand
	Magnesium Stearate	0.700	Dr. Paul Lohman, Germany
Total		**234.500**	

dried granules by using Sodium Starch Glycolate, purified talc, magnesium Stearate. Then compress the available granules by using 16 station compression machines.

Preparation of Tablet of Formulation F2 (Experiment-1, 2 & 3)

In Case of Using 20 Sieving Mesh SS Screen

The tablet was prepared by wet granulation. During wet granulation crospovidone (Kollidon-CL) and maize starch mix with water to make paste. Then paste mix with previous mixed powder of azithromycin Dihydrate, colloidal Silicon Dioxide, microcrystalline Cellulose and povidone (K-90). Before lubrication pre-screen the dried granules through 20 mesh SS screen fitted with vibratory sifter and crush the oversized granules by using fitted with 0.093"/0.065" SS screen. Then blend the available dried granules by using sodium starch glycolate, sodium lauryl sulfate, purified talc and magnesium Stearate. Then compressed the available granules by using 16 station compression machines.

In Case of Using 22 Sieving Mesh SS Screen

Process as above mentioned way of sieving through 20 but before lubrication pre-screen the dried granules through 22 mesh SS screen fitted with vibratory sifter and crush the oversized granules by using fitted with 0.093"/0.065" SS screen. Then blend the available dried granules by using sodium starch glycolate, sodium lauryl sulfate, purified talc and magnesium Stearate. Then compressed the available granules by using 16 station compression machines.

In Case of Using 24 Sieving Mesh SS Screen

Process as above mentioned way (22 mesh)but before lubrication pre-screen the dried granules through 24 mesh SS screen fitted with vibratory sifter and crush the oversized granules by using fitted with 0.093"/0.065" SS screen. Then blend the available dried granules by using sodium starch glycolate, sodium lauryl sulfate, purified talc and magnesium Stearate. Then compressed the available granules by using 16 station compression machines.

Preparation of Tablet of Formulation F3 (Experiment-1 & 2)

In Case of Using 30 Sieving Mesh SS Screen

The tablet was prepared by wet granulation. During wet granulation suspend maize starch into hot water to make paste. Then paste mix with previous mixed powder of triamterene, hydrochlorothiazide, lactose, microcrystalline Cellulose, starch 1500 and maize starch. Before lubrication pre-screen the dried granules through 30 mesh SS screen fitted with vibratory sifter and crush the oversized granules by using fitted with 0.093"/0.097 SS screen with knives and pass through 30 mesh SS screen. Then blend the available dried granules by using sodium starch glycolate, sodium lauryl sulfate, purified talc and magnesium Stearate. Then compressed the available granules by using 16 station compression machines.

In Case of Using 40 Sieving Mesh SS Screen

Process as above mentioned way (30 mesh) but before lubrication dried granules was pre-screen the dried granules through 40 mesh SS screen fitted with vibratory sifter and crushed the oversized granules by using fitted with 0.093"/0.097 SS screen and again pass the crushed granules through 40 mesh SS screen and followed as above mentioned process or then blend the available dried granules by using sodium starch glycolate, sodium lauryl sulfate, purified talc and magnesium Stearate. Then compressed the available granules by using 16 station compression machines.

Evaluation of Tablets

Weight and weight variation

A small variation does not ensure good content uniformity between dosage units a large; weight variation precludes good content uniformity. (Dittert.1974).

Thickness

At constant compressive load, tablet thickness varies with changes in die fill and tablet weight, with constant dies fill. Thickness varies with variations in compressive load. Some variation in tablet thickness is a particular lot of the tablet

or between different lots of the product is inevitable. In practice the crown thickness of individual tablets may be measured with a micrometer of five or ten tablets may be simultaneously measured in holding tray with a sliding scale. In general tablet thickness is controlled within 5% of a standard value. Tablets thickness control may be impossible unless 1. The physical properties of raw material are closely controlled, 2. The upper and lower punch lengths are accurately and continuously standardized and the granulation properties, including density, particle size and particle distribution are also carefully controlled, tablet thickness cannot be controlled. Independently since it is related to tablet weight, compaction, density, friability, and possibly drug release and bioavailability. (Dittert.1974)

Hardness

Tablet hardness is usually expressed as the load required to crush a tablet placed on its edge. Hardness is sometimes termed the tablet crushing strength.

Most manufactured consider a tablet hardness of about 5 kg to be minimal for uncoated tablet. The hardness of a tablet is a function of the compressive force, the granules or crystal hardness and ability to deform under load. The binder used and their concentration, the granulation method. (Dittert.1974).

Friability

Tab friability results in weight loss of tablet in the package container, owning to partial powdering, chipping, or fragmentation of the tablets on attrition or wear. Cotton or other cellulose materials are commonly placed in containers of tablets to keep them tightly packed to reduce railing and fractional contact on shipping or other handling and agitation. A laboratory tester has been developed to quantify tablet friability. The friability has a plastic chamber that is revolved at 25r.p.m, dropping the tablets a distances of 6 inches with each revolution. Normally reweighed the tablet sample is placed in the friabilator which is operated for 100 revolutions, after which the tablets are reweighed. Conventional compressed tablets that the loss than 0.5 to 1.0 percent in weight on friabilator testing are usually considered acceptable. Tablet friability may be profoundly affected by the moisture content of the tablet granulation and finished tablets. Very dry granulation and tablets containing less than 0.5 to1.0 percent of moisture may be much more friable than tablets containing 20to 4 % of moisture. (Dittert.1974).

Disintegration

The United States pharmacopoeia has long had a disintegration test for tablets. The U.S.P apparatus employees 6 glass tubes, 3 inches long open at the top end and against a 10 mesh screen at the bottom end of the basket rack assembly in practice, one tablet is placed in each tubes and the basket rack is positioned in a 10litre beaker of water. Simulated gastric fluid, or simulated intestinal fluid at 37 ± 20 such that the tablets remain at least 2.5 cm. From the bottom of the beaker. A standard motor driven device is used to move the basket rack assembly containing the tablets up and down of 28 to 32 cycles per minute.(Dittert.1974).

Dissolution

Drugs administered orally on solid dosage form must dissolve in the contents of the gastrointestinal tract before drug absorption can occur. Often the rate of drug absorption is determined by the of drug dissolution from the dosage form. Dissolution test equipments and condition for formulation F1, F2 and F3 are detailed in table no.3.3

Dissolution Method of Formulation F1 Procedure

900 ml medium was placed in the dissolution vessel. Assembled the apparatus and warm the media at 37^0C ± 0.5^0C. Then weighed and placed one tablet in each vessel, immersed the paddle in the media to distance of 2.5 ± 0.2 cm between the paddle and the bottom of the vessel and operate the apparatus at 50 rpm. After 45 minutes withdraw 25 ml of solution & filtered through Whatman no. 1 filter paper.

Table 3.3: Dissolution test equipments and condition for formulation F1, F2 and F3

Used equipment & Condition	Formulation F1	Formulation F2	Formulation F3
Apparatus	II (paddle)	II (Paddle)	II (Paddle)
RPM	50	75	75
Wavelength	287 nm	Not applicable	262 nm (for hydrochlorothiazide) and 357 nm (for triamterene)
Temperature	$37^0C \pm 0.5^0C$	37 ± 0.5^0C	$37^0C \pm 0.5^0C$
Time	45 minutes	45 minutes	30 minutes
Medium	1% Sodium Lauryl Sulfate in water	pH 6.0 sodium phosphate buffer	0.1 N HCl
Reagent	0.1 N HCL of Merck KGaA, Germany	Sodium phosphate buffer of Merck KGaA, Germany	0.1 N HCL of Merck KGaA, Germany
Instrument	CTO-10 AS VP of Shimadzu HPLC	CTO-10 AS VP of Shimadzu HPLC	Erweka dissolution tester of Germany
Limit of specification	Not less than 75%	Not less than 75%	Not less than 80% USP

Further diluted 5 ml to 50 ml with buffer and mixed well.

Standard Preparation

10 mg Etoricoxib WS was accurately weighed and taken into 50 ml volumetric flask. Added 1-2 ml of Methanol and volume to 50 ml with buffer (1% Lauryl Sulfate) & filtered through Whatman no. 1 filter or equivalent filter paper. Further diluted 2.5 ml filtrate to 50 ml with buffer.

The absorbance was measured at 287 nm using buffer as blank.

Calculation

$$\frac{\text{Dilution x Std. Wt. (mg) x Asmp x std. Pot. (\%) x Av. Wt. (g) of tablet}}{\text{Tablet wt. (g) x Dilution X Astd X Claim (mg)}} = \text{\% dissolved.}$$

Dissolution Method of Formulation F2

Procedure

The medium was placed in the vessel, assembled the apparatus and warmed the medium to 37 ± 0.5^0C. One tablet was weighed and placed in each vessel, immersed the paddle into the media to maintain the distance of 2.5± 0.2 cm between the paddle & the bottom of the vessel and operated at 75 rpm. After 45 minutes, 20ml solutions was withdrawn & filtered a portion of the solution through a filter having porosity of 0.5 µm or less. 2.0 mL of the filtrate was transferred to a 25-mL volumetric flask, diluted with Mobile phase to volume, and mixed. 2.0 mL of this solution was transferred to a second 25-mL volumetric flask, diluted with Mobile phase to volume, and mixed. (Sample solution)

About 14 mg of USP Azithromycin RS / WS accurately weighed, and transferred to a 50-mL volumetric flask. 25 mL of Dissolution Medium

was added and sonicated briefly to dissolve. Diluted with Dissolution Medium to volume, and mixed. 2.0 mL of this solution was transferred to a 25-mLvolumetric flask, diluted with Mobile phase (prepared as directed in the Assay) to volume, and mixed. 4.0 mL of this solution was transferred to a second 25-mL volumetric flask, diluted with Mobile phase to volume, and mixed.(Standard solution)

Preparation of Phosphate Buffer

6 liters of 0.1 M dibasic sodium phosphate was prepared by dissolving 85.2 g disodium hydrogen phosphate in 6 liters water. pH 6 ± 0.05 was adjusted with about 40 ml conc. HCl, add 600 mg trypsin and mixed well. (NOTE: Using water having resistivity of NLT 18 M ohm-cm). (United states pharmacopoeia, 2008.)

Dissolved the amount of Azithromycin was determined by employing the procedure set forth in the assay, making any necessary modification.

Calculation

Dilution x Std. wt (mg) x Sample peak area x STD Potency (%) as base x Av. tablet wt

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Tablet wt. (g) x Dilution x Standard peak area x Claim (mg)

= % of Azithromycin dissolved

Dissolution Method of Formulation F3

Procedure

900 ml medium was placed in the dissolution vessel. Assembled the apparatus and warm the media to 37^0C ± 0.5^0C. Weigh and place one tablet in each vessel, immerse the media to distance of 2.5 ± 0.2 cm between the paddle and the bottom of the vessel and operate the apparatus at 75 RPM. After 30 minutes withdraw 25 ml of the solution & filter through Whatman No. 1 filter paper. Diluted 5 ml of filtrate to 50 ml with the same medium.

Standard Preparation

HTZ (10.0 mg) & TMT (20 mg) RS / WS accurately weighed and taken in a 100 ml volumetric flask. Added about 70 ml of 0.1 N HCl, warm, shook well mechanically for 10 minutes and volume up to 100 ml with 0.1 N HCl, mixed and filtered through Whatman No. 1 filter paper. Dilute 2.5 ml to 100 ml with 0.1 N HCl and mix.

The absorbance of the sample and standard solution was measured at 262 nm (for hydrochlorothiazide) and 357 nm (for triamterene) using 0.1 N HCl as blank.

Calculation

% Hydrochlorothiazide dissolved =

Dilution x Std. wt. (mg) x Asmp. x Std. potency (%) of Hydrochlorothiazide x Av. wt.(g) of tablet

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Sample wt (g) x Dilution x Astd. x Claim (mg)

% Triamterene dissolved =

Dilution x std. wt. (mg) x Asmp. x Std. potency (%) of Triamterene x Av. wt. (g) of tablet

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Sample wt (g) x Dilution x Astd. x Claim (mg)

Potency Determination or Assay

Assay is the content of active ingredients that an unit dose contains. Assay test equipments and condition for formulation F1, F2 and F3 are detailed in table no.3.4

Assay Method of Formulation F1

Standard Preparation

Accurately weighed and transferred 10 mg Etoricoxib WS into a 50 ml volumetric flask and diluted to volume with Methanol. Sonicated for 5 minutes with periodical shaking. Filter through Whatman no. 1 filter paper. Further diluted 2.5 ml filtrate to 50 ml with Methanol and mix.

Sample Preparation

Accurately weighed and transferred 20 mg of finely powdered blend (equivalent to 10 mg Etoricoxib) into a 50 ml volumetric flask and diluted to volume with Methanol. Sonicated for 5 minutes with periodical shaking. Filtered through Whatman no. 1 filter paper or equivalent filter paper. Further diluted 2.5 ml filtrate to 50 ml with Methanol and mixed.

Table 3.4: Assay test equipments and condition for formulation F1, F2 and F3

Used equipment& Condition	Formulation F1	Formulation F2	Formulation F3
Glass apparatus/ accessories	Volumetric flask, Pipette, Whatman no. 1 filter paper		Volumetric flask, Pipette, Whatman no. 1 filter paper
Instrument	UV 1601 (PC) S of Shimadzu Corporation, Japan and Sartorius Electronic Balance of Germany	UV 1601 (PC) S of Shimadzu Corporation, Japan and Sartorius Electronic Balance of Germany	UV 1601 (PC) S of Shimadzu Corporation, Japan and Sartorius Electronic Balance of Germany
Reagent	Methanol	Acetonitrile	glacial acetic acid and 0.1 M NaOH
Limit of specification	81.00-99.00mg / tablet(As per INN)	490.0-510.0 mg/tab	47.5 -52.50 mg triamterene /tablet,23.75-26.25mg Hydrochlorothiazide/ tablet

The absorbance was measure at 284 nm using methanol as blank.

Calculation

Dilution x Std wt (g) x Asmp X Std. Potency (mg/g) x Av. Core Wt

Sample wt. (g) x Dilution X A std

= mg of Etoricoxib per tablet

Assay Method of Formulation F2

Column and Condition

Packed with end-capped polar-embedded octadecylsilyl amorphous organo silica polymer R (Waters Xterra RP_{18}), Dimension - 250 mm X 4.6 mm X 5 µm, Temperature -70^{O}C, Wavelength (λ)- 215 nm, Flow rate - 1.0 ml/min, Injection Volume -70 µl

Mobile Phase

5.8 g of monobasic potassium phosphate was dissolved in 2130 mL of water, add 870 mL of Acetonitrile, and mixed. Adjust with about 6 mL of 10 N potassium hydroxide to a pH of 11.0 ± 0.1, and pass through a filter having a 0.5-µm or finer porosity, and degas. Necessary adjustments necessary was made.

Standard Stock Preparation

About 16.5 mg of USP Azithromycin RS / WS, accurately weighed, was transferred to a 100-mL volumetric flask, 10 mL of acetonitrile was added, and dissolved by swirling and with the aid of brief sonication and finally diluted with acetonitrile to volume, and mixed.

Standard Preparation

2.0 mL of the Standard stock preparation was transferred to a 100-mL volumetric flask, diluted with Mobile phase to volume, and mixed to obtain a Standard preparation having a known concentration of about 0.0033 mg of USP Azithromycin RS per mL.

Sample Preparation

Fine powder not less than 20 tablets was weighed and transferred (accurately weighed portion of the powder about 330 mg, equivalent to about 250 mg of Azithromycin) to a 250-mL volumetric flask.

Then about 175 mL of acetonitrile was added and shook by mechanical means for 30 minutes. Diluted with acetonitrile to volume, and mixed. About 40 mL of the resulting suspension placed in a centrifuge tube, and centrifuge. 2.0 mL of

the clear supernatant liquid was transferred to a 50-mL volumetric flask, diluted with Mobile phase to volume, and mixed. 2.0 mL of this solution was transfer red to a 25-mL volumetric flask, diluted with Mobile phase to volume, and mixed.

Resolution Solution

About 8 mg of USP Azaerythromycin A RS was transferred to a 50-mL volumetric flask, 5 mL of acetonitrile was added, and dissolved by swirling and with the aid of brief sonication. Diluted with Mobile phase to volume, and mixed. 2.0 mL of the solution so obtained and 2.0 mL of the Standard stock preparation was transferred to a 100-mL volumetric flask, diluted with Mobile phase to volume, and mixed.

Chromatographic System

The liquid chromatograph is equipped with an amperometric electrochemical detector with dual glassy carbon electrodes operated in the oxidative screen mode with electrode 1 set at +0.70 ± 0.05 V and electrode 2 set at +0.82 ± 0.05 V, and the background current optimized to 85 ± 15 nanoamperes, a 4.6-mm × 5-cm guard column that contains 5-µm packing L29 and a 4.6-mm × 15-cm analytical column that contains 5-µm packing L29 or 3-µm packing L49 without the guard column. The flow rate is about 1.5 mL per minute.

Chromatograph the resolution solution, and record the responses as directed for Procedure: the relative retention times are about 0.7 for azaerythromycin A and 1.0 for Azithromycin with the L29 column and about 0.8 for azaerythromycin A and 1.0 for Azithromycin with the L49 column; and the resolution, R, between azaerythromycin A and Azithromycin is not less than 2.5. Chromatograph the Standard preparation, and record the responses as directed for Procedure: the tailing factor for the Azithromycin peak is not less than 0.9 and not more than 1.5; the column efficiency is not less than 1000 theoretical plates; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure

Separately equal volumes (50µl) of the standard and the sample preparation were injected into the chromatograph, the peak responses for the Azithromycin was recorded. The amount of Azithromycin was Calculated using the following formula -

$$\frac{\text{Dilution x Std. wt (g) x Sample peak area x Std. potency as base (mg/g) x Av. tablet wt. (g)}}{\text{Sample wt. (g) x Dilution x Std. peak area}}$$

= mg of Azithromycin / tablet

Assay Method of Formulation F3

Formulation F3 contained three active pharmaceutical ingredients. They were Triamterene, Hydrochlorothiazide and 5 - Nitroso - 2,4,6 – triaminopyrimidine. Assay procedure of Triamterene and Hydrochlorothiazidehas been discussed and their result was recorded.

Triamterene Content

Accurately about 110 mg powder was weighed and taken (equivalent to 20 mg triamterene) into 100 ml volumetric flask containing about 10 ml of a mixture of equal quantity of glacial acetic acid & water (1:1) with the aid of gentle heat, cooled and added water up to 100 ml . Mixed and filtered through Whatman No.1 filter paper.

Diluted 1 ml to 50 ml with 1 M acetic acid and mixed well. A reference / working standard (by taking 20 mg triamterine) was prepared in the same way to obtain similar concentration. The absorbance of both sample and standard solution was measured at 360 nm using 1 M acetic acid as blank.

Calculation

$$\frac{\text{Dilution x Std. wt. (g) x A sample x Std. potency (mg/g) as Triamterene x Av. wt. (g)}}{\text{Sample wt (g) x Dilution x Astd.}}$$

= mg Triamterene / tablet (Claimed as 50.00 mg triamterene / tablet)

Hydrochlorothiazide Content

Accurately about 110 mg of the powdered tablets (equivalent to 10 mg hydrochlorothiazide) was weighed and taken into a 100 ml volumetric flask. About 50 ml of 0.1 M NaOH was added and shook mechanically for 20 minutes, diluted to volume with 0.1 M NaOH, mix and filtered through Whatman No.1 filter paper. Diluted 5 ml of the filtrate to 50 ml with water & mixed well. A reference /working standard was prepared (by taking 10 mg HTZ) similarly. The absorbance of the sample & standard solution in was determined 1 cm cell at 273 nm using water as blank.

Calculation

$$\frac{\text{Dilution x Std. wt. (g) x Asample x Std. potency.(mg/g) as Hydrochlorothiazide x Av. wt. (g)}}{\text{Sample wt (g) x Dilution x Astd.}}$$

= mg Hydrochlorothiazide / tablet (Claimed as**:** 25.00 mg hydrochlorothiazide / tablet)

RESULTS AND DISCUSSION

Physical and chemical evaluation of prepared tablets of three different formulations processing granules through different size of mesh have been presented below-

Physical and chemical evaluation of tablet of Formulation F1 (Experiment1, Experiment 2 & Experiment 3) is presented in the table 4.1.

Variations in the ratio of small to large granule sizes and magnitude of difference between sizes influence void spaces between particles are filled. Thus, although the apparent volume in the die is essentially same, different proportion of large particle and small particle may change the weight to fill a small die cavity, relatively few granules are required and the difference of only a few granules around the average may represent a high percentage weight variation. If hundreds of granules are required on the average for die fill, a variation of a few granules around the average would produce a minor weight variation, given a narrow size range. (Lachman et al., 1987 and Patrick, 2006). Tablet weight of formulation F1 is 180 mg. So, granules size should be Coarse to obtain the desire physical and chemical properties. After observing result of Table 4.1, 4.2 & 4.3, it was found that most of evaluating parameters are better if 22 sieving mesh is used compare to other. But, in case of 30 sieving mesh, the physical appearance is not good due to finer particle but dissolution is slightly better. On other hand, in case of 40 sieving mesh, moderately coarse particles produced and finally produced problematic tablet with sticking but dissolution is better.

Physical and chemical evaluation of tablet of formulation F2 (Experiment 1, Experiment 2 and Experiment 3) is given in the table 4.2.

Tablet weight of formulation-2 is 660 mg. So, granules size should be Coarse to obtain the desire physical and chemical properties. After observing result of Table 4.2, it was found that most of evaluating parameters are better if 22 sieving mesh is used compare to other. But, in case of 20 sieving mesh, tend to capping has found due to coarser particle & also dissolution is slightly less. On other hand, in case of 40 sieving mesh, moderately coarse particle is produced and finally produced problematic tablet with sticking but dissolution is better.

Physical and chemical evaluation of tablet of formulation F3 (Experiment 1& 2) is given in the table No. 4.3.

Tablet weight of formulation-3 is 234.500 mg. So, granules size should be slightly coarse to obtain the desire physical and chemical properties. After observing result of Table 4.3, It was found that most of evaluating parameters are better if 30 sieving mesh is used compare to 40 sieving mesh. But, in case of 40 sieving mesh, the physical appearance is not good due to moderately coarse particle but dissolution is slightly better. On other hand, in case of 40 sieving mesh, problematic tablet has produced due to sticking & capping. In manufacturing of this product, compatible nature of active materials should be strictly considered because it contains two different active.

Table 4.1 Tablet's quality property of Formulation F1of Experiment 1, 2 &3

Experiment No.	Sieving mesh size	Physical or chemical parameter	Result	Specification
1	22	Appearance	**Complies**(found no defect i.e. sticking, picking, black spots, streaks, lamination, capping)	Off white oval biconvex tablet.
3	30		Found less glassy & tend to sticking and no other defect i.e. picking, black spots, streaks, lamination, capping	
3	40		Found sticking & no other defect i.e. picking, black spots, streaks, lamination, capping	
1	22	Hardness	5.91-8.46	3.00 -15.00
2	30		5.91-7.85	
3	40		5.91-7.44	
1	22	Thickness	3.54-3.60	3.20 -4.00
2	30		3.60-3.62	
3	40		3.60-3.64	
1	22	Average wt. of 20 tablets.	180	167 -193
2	30		181	
3	40		178	
1	22	Disintegration time	1.18-1.46	NMT 15 minute with disc.
2	30		1.02-1.35	
3	40		1.17-2.02	
1	22	Friability	0.14%	NMT 1%
2	30		0.18%	
3	40		0.25%	
1	22	Dissolution	91-93%	Not less than 75% dissolved in 45 minutes.
2	30		93-97%	
3	40		96-101%	
1	22	Assay	87.66	(81.00-99.00)mg/tab
2	30		89.93	
3	40		90.01	

Table 4.2: Tablet's quality property of Formulation F2 of Experiment 1, 2 & 3

Experiment No.	Sieving mesh size	Physical or chemical parameter	Result	Specification
1	20	Appearance	**Complies** (found no defect i.e. sticking, picking, black spots, streaks, lamination, capping)	Off white Circular biconvex normal tablet.
2	22		**Complies** (found no defect i.e. sticking, picking, black spots, streaks, lamination, capping)	
3	24		Found sticking & no other defect i.e. picking, black spots, streaks, lamination, capping	
1	20	Hardness	13.25-16.21	12.0-40.0 kp
2	22		12.50-16.00	
3	24		13.46-18.04	
1	20	Thickness	6.13-6.22	6.10-6.70 mm
2	22		6.18-6.22	
3	24		6.17-6.24	
1	20	Average wt. of 10 tablets	659	644-676 mg
2	22		662	
3	24		660	
1	20	Disintegration time	10.57-12.35	NMT 15 minute with disc.
2	22		9.0-11.23	
3	24		10.12-11.69	
1	20	Friability	0.28%	NMT 1%
2	22		0.25%	
3	24		0.32%	
1	20	Dissolution	93-97%	Not less than 75%(Q) dissolved in 45 minutes
2	22		97-102%	
3	24		96-103%	
1	20	Assay	495.88 mg	(490.0-510.0)mg/tab
2	22		496.25 mg	
3	24		498.28 mg	

Table 4.3: Tablet's quality property of Formulation F3 of Experiment 1 & 2

Experiment No.	Sieving mesh size	Physical or chemical parameter	Result	Specification
1	30	Appearance	**Complies** (found no defect i.e. sticking, picking, black spots, streaks, lamination, capping)	Light yellow RFBE tablet
2	40		**Not Complies** (found sticking & capping but no other defect i.e. picking, black spots, streaks, lamination)	
1	30	Hardness	7.44-8.26	3.50-13.00 kp
2	40		7.80-8.50	
1	30	Thickness	3.0-3.04	2.70-3.20
2	40		3.0-3.04	
1	30	Average wt. of 10 tablets.	272	265-279
2	40		272	
1	30	Friability	0.38	NMT 1%
2	40		0.06	
1	30	Disintegration time	3.02-3.45	NMT 15 (With disc)
2	40		3.16-3.56	
1	30	Dissolution	Triamterene: (79-90)%	Not less than 80 % in 30 minutes
			Hydrochlorothiazide: (81-97)%	
2	40		Triamterene: (70- 78)%	
			Hydrochlorothiazide: (72-80)%	
1	30	Assay	Triamterene: 49.82mg	Triamterene**:** (47.50 – 52.50) mg/tablet And Hydrochlorothiazide: (23.75– 26.25) mg/tablet
			Hydrochlorothiazide:25.98 mg	
2	40		Triamterene: 50.82mg	
			Hydrochlorothiazide:25.05 mg	

CONCLUSION

At present, the study of sieving meshes in pharmaceuticals to control smooth and effective production is very significant. The approach of this study was to make a comparative evaluation of tablets of different particle size of available existing sieving mesh. The study reveals that, the physical and chemical properties of observing formulated tablet was changed with the changes of particle size of materials through sieving with different mesh. The data shows that less weighted tablet require relatively small size particles of more openings in sieving mesh and more weighted tablet require relatively moderate sized particles of less size of openings sieving mesh. Physiochemical properties of tablet are depended and also determined by the sieving mesh & process involved. It's a wide area to research, where a lots of option is open to contribute in future. But, the future goal of this study is to identify the right sieve to get the optimum tablet's physic-chemical property which may ensure proper processing and quality of product. Approaches may be developed to adjust physiochemical properties of tablet with readily available sieving mesh to evaluate cost effective processing with entire good quality. This research might be a platform for further investigation in this area.

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