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EFFECT OF COMPACTION PROCESS IN GRANULOMETRY

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ABSTRACT: Quetiapine is indicated for the treatment of schizophrenia as well as for the treatment of acute manic episodes associated with bipolar I disorder. The aim of the present study is to evaluate the effect of manufacturing process on critical quality attribute on In-process parameters (Granules). Quetiapine fumarate was selected as a model drug for sustained release drug delivery system manufactured by wet granulation process [1]. To identify the effect of compacted Magnesium Oxide Light in the release behavior of model drug. During the study different percentage of Magnesium Oxide light compacted and granulated by using dichloromethane as granulating solvent. Other excipients with different functionality were added in the formulation such as Microcrystalline Cellulose, Lactose monohydrate, Controlled release polymer Carrageenan, Povidone and Magnesium stearate. Initially Magnesium Oxide light was compacted by using vertical type Roller compactor. From the compacted material 40%- 50% screened & 50%-60% retained over #60 mesh is optimized ratio, and this ratio must be maintained to get the targeted release of the said drug from the final uncoated Tablet. To find the release profile of the model drug, Citrate Phosphate buffer at pH 6.4-6.6 with volume 1000ml was selected as dissolution media, apparatus used is USP 2 with stationary basket.

INTRODUCTION: Granulometry plays very significant role in controlling dissolution of certain drugs Particularly in extended release matrix tablets [2], in present study compaction behavior of one of the ingredient Magnesium oxide light and its particle size distribution for controlling dissolution rate of model drug with constant polymer composition has been studied, release of drug from matrix tablet depends on gelling/erosion/diffusion pattern but compacted ingredients with their defined particle size range also has its major impact on controlling drug release for certain kind of drugs. [3, 4]

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In the present study model drug selected is Quetiapine fumarate and is a psychotropic agent belonging to a chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo [b, f] [1, 4] thiazepin-11-yl-1-piperazinyl) ethoxy]-ethanol fumarate (2:1) (salt). It is present intablets as the fumarate salt. The Quetiapine Fumarate indicated for the acute andmaintenance treatment of schizophrenia, bipolar mania and bipolar depression, Since site of action of Quetiapine is CNS, so drug reaching to the site must be controlled for prolong period of time. [5, 6] Therefore, the objective of the present work is to provide a long acting pharmaceutical composition with one of the compacted ingredient within certain particle size containing Quetiapine fumarate in a sustained release matrix formulation [7], to maintain the blood levels of the active ingredient for a prolonged period of time and to avoid dose dumping.

MATERIALS AND METHODS:

Materials:

Quetiapine Fumerate API was procured from Medichem, Europe. Microcrystalline Cellulose was procured from JRS Pharma, Lactose was procured from Light Magnesium Oxide was procured from Merck, Carrageenan Lanbda from FMC, Povidone from ISP, Methylene Chloride from Finar, Magnesium Stearate from Peter greven, Titanium dioxide from Kronos international

Preparation of matrix tablets:

Tablets prepared by wet granulation process. In all cases, the amount of the active ingredient was 400 mg and the total weight of the tablet was 1200 mg. The batch composition is as in **Table 1**

During tableting process, First magnesium oxide light is compacted using roller compactor at varying roller compaction parameters (**Table 2**) to obtain magnesium oxide of different granulometry ratio coded as A, B, C and D. Each of these compacted coded magnesium oxide granules is introduced along with constant composition of excipients and Quetiapine Fumarate into the wet granulation process. The solution of PVP K-30 in Methylene chloride as a granulating agent. The granulated material is dried in Fluid bed dryer followed by milling till desired critical material attribute is achieved for granules. The milled granules are lubricated with extra-granular magnesium stearate for specified time interval in a lab scale blender. The particle size distribution of lubricated granules is as reported in Table 4. Using D-Type punch tooling the compression is performed in 10 station compression machines. All the preparations stored in airtight containers at room temperature for further study.

TABLE 1: FORMULA COMPOSITION

Ingredients	Trial No A	Trial No B	Trial No C	Trial No D
Quetiapine Fumarate	460.52	460.52	460.52	460.52
Magnesium Oxide Light Compacted (a)	180	-	-	-
Magnesium Oxide Light Compacted (b)	-	180	-	-
Magnesium Oxide Light Compacted (c)	-	-	180	-
Magnesium Oxide Light Compacted (d)	-	-	-	180
Microcrystalline cellulose	59.74	59.74	59.74	59.74
Lactose Monohydrate	59.74	59.74	59.74	59.74
Carrageenan	300	300	300	300
Povidone K30	120	120	120	120
Methylene chloride	qs	qs	qs	qs
Magnesium Stearate	20	20	20	20
	1200	1200	1200	1200

TABLE 2: ROLLER COMPACTION PARAMETER

Parameter	Set Value
Roller Speed	12-15 rpm
Roller gap	1.5-2.0 mm
Hydraulic Pressure	55-60 bar
Pregranulator speed	100-120 rpm
Fine granulator speed	120-130 rpm
Feed screw speed	20-25 rpm

Evaluation of Granules properties:

The compacted granules of Magnesium oxide and final granules after wet granulation were evaluated for particle size distribution. The particle size distribution was conducted using Sieve shaker apparatus.

Control tests for matrix tablets:

Different formulation (Trial no.A to Trial no.D) Evaluated for hardness, weight variation, thickness and friability. Hardness of 10 matrix tablets from each formulation measured using Hardness tester (**Erweka GMBH,** TBH125 model, Germany). Friability of the tablets was determined by testing 10 tablets in a Tianjin Jing TuoYiqiCS2 for 4 minutes at 25 rpm. A slide calipers had used to measure the thickness for 5 tablets. Weight variation test has performed by taking 10 tablets using an electric balance (Metler Toledo) according to the official method.

Dissolution testing:

Dissolution studies were performed using the USP I, Basket-rotating method (Electro lab dissolution tester, TDT-08, India) at 37 °C ± 0.5 °C and 2000 rpm using 0.1 N HCl in the initial 5 hours with 900 ml and phosphate buffered solution, pH 6.8 (PBS) till the end of the study [7] at 1000 ml, as the dissolution media. A 2 ml aliquot of sample was withdrawn at regular time intervals, filtered and then these samples were diluted 10 folds with distilled water and then assayed using High performance liquid chromatography. The cumulative % drug release was calculated for the formulations.

***In vitro* dissolution study of tablets:**

Dissolution studies were shown using a tablet dissolution apparatus-II, **Hanson Vision G2,** type 2 (paddle with stationary basket), in 1000 mL, citro-phosphate buffer pH 6.4-6.6 at 37.5°C ± 0.5°C and stirring speed was 100 rpm. During dissolution, 10 ml of sample has taken and same amount replaced to maintain sink condition than that sample was filtered with filter paper than, the sample solution was analyzed at 250 nm for Quetiapine fumarate by UV spectrophotometer (Shimadzu 1240, UV visible spectrophotometer, Japan).

The dissolution study was continued for 24 hours, the in-vivo condition and drug dissolved at identified time periods was plotted as percent release versus time (hours) curve. The targeted release specification was set as in **Table 3;**

TABLE 3: TARGET DISSOLUTION RELEASE SPECIFICATION

Sampling Time points	% drug release
2hrs	NMT 20%
7hrs	45% - 65%
24hrs	NLT80%

RESULTS AND DISCUSSION:

The ER tablets of Quetiapine Fumarate were prepared as there was no literature available on the prepared dosage form and Quetiapine Fumarate was a drug of choice in case of many psychotic patients. Dry granulation was the prepared technique for making SR formulations, as the other techniques did not give satisfactory flow properties due to the fluffiness of the drug.

Physical Evaluation of Quetiapine fumarate tablets:

The tablets of the projected formulations (Trial A to Trial D) evaluated for hardness, weight variation, thickness and friability. The thickness ranged from 6.41 to 6.55 mm. The hardness ranged from 230 to 250 N The %friability of all trials is less than 0.1%,. The average percentage weighted deviation of 10 tablets of each formula was less than 5%.

Granules Properties:

The compacted Magnesium oxide and lubricated final granules were evaluated for particle size distribution. The results are compiled in **Table 4** and **Table 5**. Particle size distribution of Magnesium oxide granules is found to be different for all the manufactured batches. The impact of different granulometry on Drug product critical quality attribute need to be studied.

TABLE 4: PARTICLE SIZE DISTRIBUTION OF MAGNESIUM OXIDE GRANULES

Code	% Pass - #60 mesh	% retain - #60 mesh
Trial No A	40-50%	50 - 60%
Trial No B	70-80%	20-30%
Trial No C	60 - 70%	40 - 30%
Trial No D	50 - 60%	40 - 50%

TABLE 5 PARTICLE SIZE DISTRIBUTION OF FINAL BLEND

Sieve	%Retained	Cumulative % Retained
#30	Nil	Nil
#40	17.5	17.5
#60	27	44.5
#80	4.5	49
#100	7.5	56.5
Base Pan	43.5	100

Effect of particle size distribution of light magnesium oxide on release profile:

Matrix tablets of Quetiapine fumarate formulated using light magnesium oxide and compacted light magnesium oxide in wet granulation technique. Different particle size distribution of light Magnesium Oxide was obtained by compaction process by using vertical roller compactor. Matrix tablet containing Quetiapine as active ingredient having Carrageenan as polymer and Light Magnesium Oxide compacted as alkalizer with particle size range from 40% - 80% with sieve #60mesh pass & #60 mesh retain 20-60%

respectively of total tablet weight in the matrix tablet with the formulation code Trial A to Trial D were prepared to evaluate the effect of this alkalizer on compaction. After manufacturing the trials shown in the **Table 1**, their dissolution studies were carried out in type 2 (paddle method), in 1000 mL, citro- phosphate buffer pH 6.4-6.6 at 37.5°C ± 0.5°C and stirring speed was 100 rpm. During dissolution, 10 ml of sample has taken and same amount replaced to maintain sink condition than that sample was filtered with filter paper than the sample solution was analyzed at 250 nm for Quetiapine fumarate by UV spectrophotometer (Shimadzu 1240, UV visible spectrophotometer, Japan).

The dissolution study was continued for 24 hours, the *in-vivo* condition and drug dissolved at identified time periods was plotted as percent release versus time (hours) curve. The Dissolution profile data is as mentioned in **Table 6**. The graphical representation of In-Vitro drug release pattern for individual formulation and an overlay of all the batches are depicted in **Fig. 1 – 5.**

TABLE 6: DISSOLUTION PROFILE DATA FOR FORMULATION WITH DIFFERENT GRANULOMETRY OF MAGNESIUM OXIDE GRANULES

Time (In hour)	% Drug release from formulation with different granulometry of Magnesium Oxide Granules			
	Trial No A	Trial No B	Trial No C	Trial No D
2	12	22	5	17
7	55	72	35	42
24	96	101	78	79

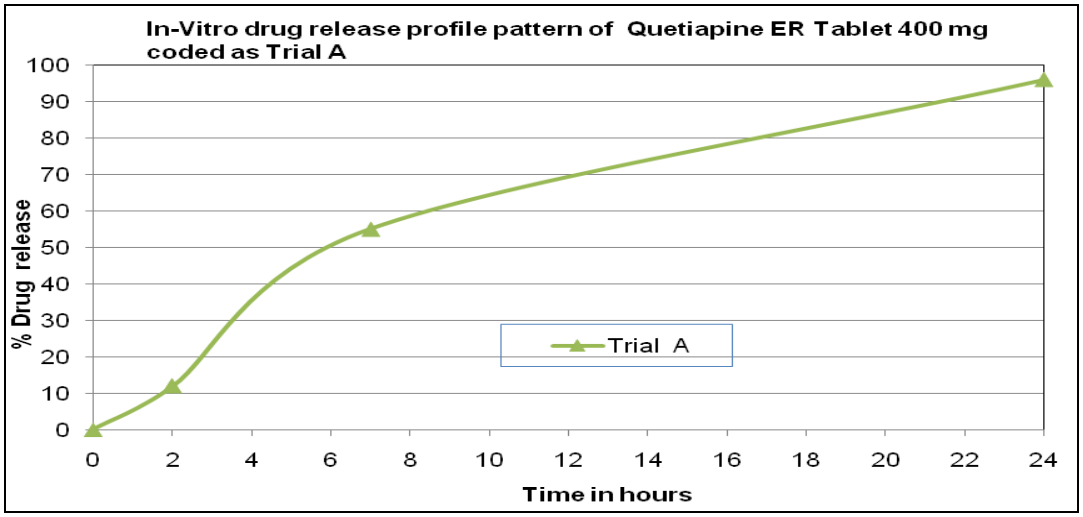

FIG.1: *IN-VITRO* DRUG RELEASE PROFILE PATTERN OF QUETIAPINE ER TABLET 400 MG CODED AS TRIAL A

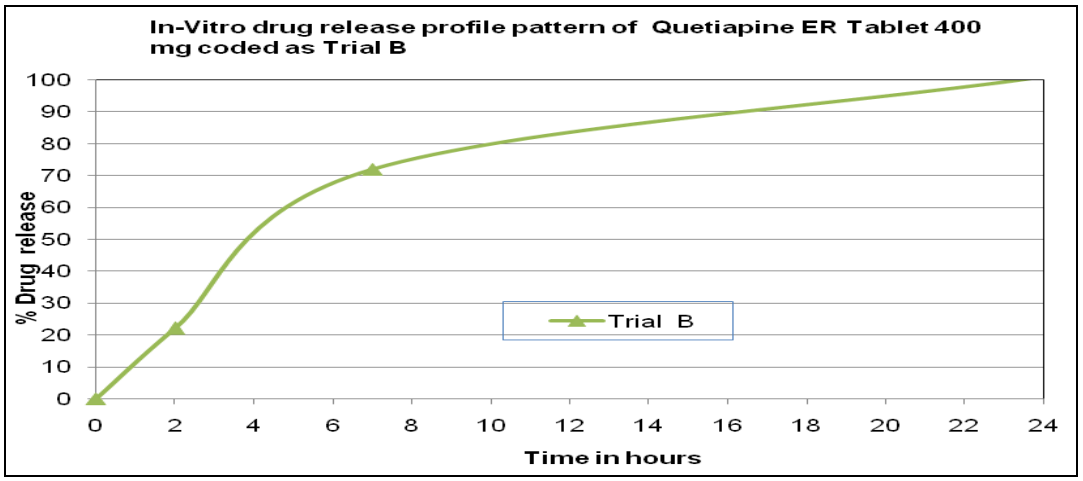

FIG. 2: *IN-VITRO* DRUG RELEASE PROFILE PATTERN OF QUETIAPINE ER TABLET 400 MG CODED AS TRIAL B

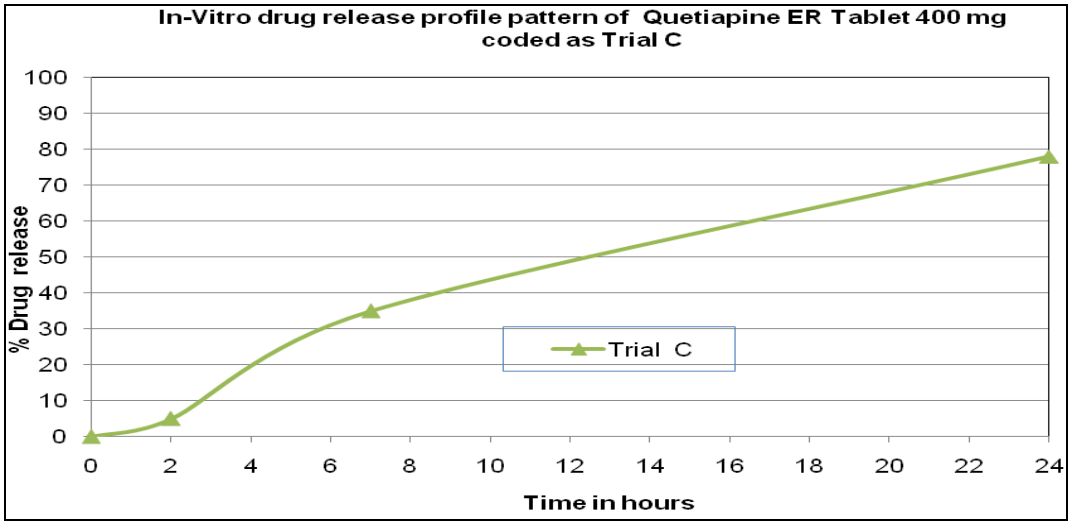

FIG. 3: *IN-VITRO* DRUG RELEASE PROFILE PATTERN OF QUETIAPINE ER TABLET 400 MG CODED AS TRIAL C

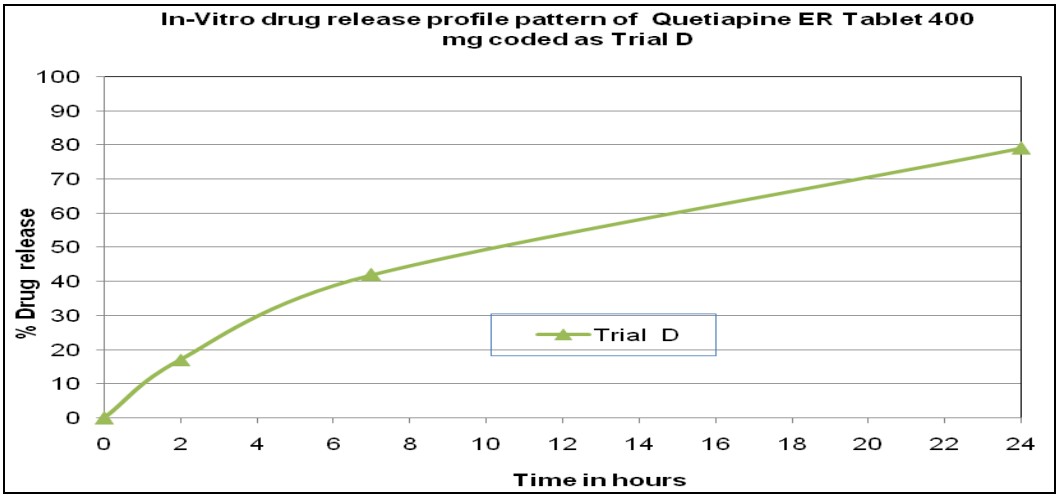

FIG. 5: *IN-VITRO* DRUG RELEASE PROFILE PATTERN OF QUETIAPINE ER TABLET 400 MG CODED AS TRIAL D

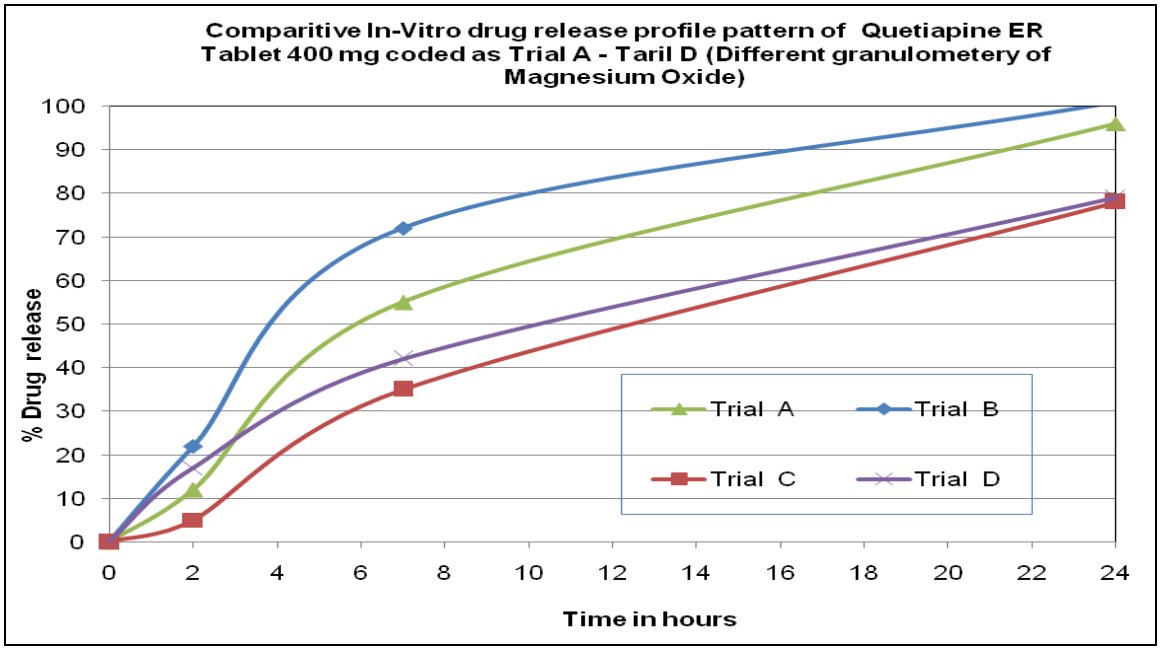

FIG.5: COMPARATIVE *IN-VITRO* DRUG RELEASE PROFILE PATTERN OF QUETIAPINE ER TABLET 400 MG CODED AS TRIAL A - TARIL D
(DIFFERENT GRANULOMETRY OF MAGNESIUM OXIDE)

CONCLUSION: In the present study Trial A with Light Magnesium Oxide Compacted with Granulometry Sieve #60 Passed 40-50%, & Sieve #60 retained 50-60% of total tablet weight formula has shown better drug release for desired release profile as compared to trials B, C and trial D. Some specific particle size range of Light Magnesium Oxide Compacted is required for its release controlling mechanism along with Polymer Carrageenan, for the model drug Quetiapine fumarate. The use of a stationary basket in the present study within a Type II dissolution apparatus leads to reduced variability in release data, is useful in collecting data for validation of models of drug release, and may have utility in studying the effects of hydrodynamics

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