The Pharma Innovation

ISSN: 2277- 7695
CODEN Code: PIHNBQ
ZDB-Number: 2663038-2
IC Journal No: 7725

Received: 16-03-2013
Accepted: 22-04-2013

Vol. 2 Issue 3 2013
Online Available at www.thepharmajournal.com

THE PHARMA INNOVATION - JOURNAL

Formulation Development And Evalution of Immediate Release Tablet of Anti Hypertensive Drug Olmesartan Medoxomile.

Dr M.M Gupta1, Mayur mahida*

1. Jaipur College of Pharmacy, Jaipur, Rajasthan, India.
[E-mail: mahidamayur2@gmail.com, Tel: +918690023577]

Olmesartan medoxomile blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT1 angiotensin II receptor. ACE inhibitor is used in treatment of hypertension. Olmesartan medoxomile tablet have been prepared by wet granulation method and also by direct compression. Effect of various fillers and disintegrants were also explored. Microcrystalline cellulose, lactose monohydrate, were used in wet granulation. In order to obtain acceptable product several trials were conducted.And ten different formulations were prepared. Various pharmacopoeial evaluations of the formulations were conducted including weight variation, hardness, disintegrationtime, friability and *in-vitro* dissolution. Final selection of formulation was done based on pharmaceutical equivalence of development formulation to that of marketed one.

Keyword: Immediate Release Tablet, Superdisintegrants, Lactose Monohydrate, Hypertension.

1. Introduction:[1-3]

The oral route of drug administration is the most popular and successfully used for conventional delivery of drugs. It offers the advantages of convenience, ease of administration, greater flexibility in dosage form design, ease of production, and lowcost. The parenteral route of administration is important in case of emergencies, whilethe topical route of drug administration recently employed to deliver drug to thespecific part of the body for systemic effect. It is probable that almost 90% of all thedrugs are administered by oral route. Tablets are solid preparations each containing a single dose of one or more active substances and usually obtained by compressinguniform volumes of particles. Tablets are intended for oral administration. Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active substance is liberated. The particles consist of one or more active substances with or without excipients such as diluents, binders, disintegrating agents, glidants, lubricants,substances capable of modifying the behavior of the preparation in the digestive tract coloring matter authorized by the competent authority and flavoring substances.The dosage form available for oral administrations are solutions, suspensions,powders, tablets and capsules. The physical state of most of the drugs being solid,they are administered in solid dosage form.

The drugs administered by oral route are versatile, flexible in dosage strength,relatively stable, present lesser problem in formulation and packaging and are convenient to manufacturer, store, handle and use. Solid dosage forms provide best protection to drugs against temperature, light, oxygen and stress during transportation.

1.1 Advantages of Tablets[1,4,6]

- They are unit dosage form, and they offer the capabilities of all oral dosage forms for the dose precision and the least content variability during dosing
- Accuracy and uniformity of drug content
- Optimal drug dissolution and hence, availability from the dosage form for absorption consistent with intended use (i.e., immediate or extended release).
- Usually taken orally, but can be administered sublingually, rectally or intravaginally.
- Their cost is lowest of all oral dosage forms
- They are the most compact of all oral dosage forms
- They are in general the easier and cheaper to package and ship as compare to other oral dosage forms
- Product identification is simple and cheap, requiring no additional processing steps when employing an embossed or monogrammed punch face
- They are ease to administer, does not require a specialist
- They are better suited to large-scale production than other unit oral forms
- They have the better properties of chemical, mechanical and microbiological stability.

1.2 Disadvantages[2]

- Some drugs resist compression, due to their amorphous nature or low-density
- Drugs having bitter taste, objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating of tablet
- Bioavailability problems.
- Chance of GI irritation caused by locally high concentrations medicament.
- Difficulty in swallowing tablets in a small proportion of people and so size and shape become important considerations.
- Slow onset of action as compared to parenterals and solutions.

1.3 Types and Classes of Tablets[1-3]

Tablets are classified by their route of administration or functions

1) Oral tablets for ingestion

- Compressed tablets or standard compressed tablets
- Multiple compressed tablets (MCT)

a) Layered tablets

b) Compression coated tablets

- Repeat action tablets
- Sustained release or modified release tablets
- Delayed action or enteric-coated tablets
- Film coated tablets
- Chewable tablets

2) Tablets used in oral cavity

- Buccal tablets
- Sublingual tablets
- Troches and lozenges
- Dental cones

3) Tablets administered by other routes

- Implantation tablets
- Vaginal tablets

4) Tablets used to prepare solutions

- Effervescent tablets
- Dispersible tablets
- Hypodermic tablets
- Tablet triturates

1.4 Introduction to Immediate Release Dosage Form[11,12]

Pharmaceutical products designed for oral delivery and currently available on the prescription and over-the-counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption. Disintegrating agents are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids. Superdisintegrant improve disintegrant efficiency resulting in decreased use levels when compared to traditional disintegrants. Traditionally, starch has been the disintegrant of choice in tablet formulation, and it is still widely used. For instance, starch generally has to be present at

levels greater than 5% to adversely affect compatibility, especially in direct compression. Drug release from a solid dosage form can be enhanced by addition of suitable disintegrants.

- Mechanism of Disintegrants:
  1) High swellability
  2) Capillary action and high swellability
  3) Chemical reaction

When introduced to an aqueous environment of use, the tablet rapidly takes up water, leading to swelling of the disintegrant and rapid disintegration of the tablet before the dispersion polymer can form a hydrogel. The disintegrant should be chosen such that it (1) swells rapidly when introduced into the use environment and (2) has a low tendency to form or promote formation of a hydrogel. The rate of swelling of the disintegrant is directly correlated to tablet disintegration times. Tablets containing disintegrants cause more rapid swelling have faster disintegration times at comparable disintegrant levels.

The amount of work, W, or swelling energy, due to swelling can be measured using a dynamic mechanical analyzer (DMA). The swelling energy attributable to swelling of the disintegrant in the compact may be calculated from the following equation:

$$W = P\Delta V$$

Where W is the work or swelling energy of the disintegrant, P is the pressure applied by the probe, and ΔV is the volume change of the sample.

To compare disintegrants, the swelling energy per mass of disintegrant is used. Preferably, the disintegrant generates a swelling energy of at least 0.05 J/g within about 10 minutes following addition of water to the liquid reservoir.

The most popular disintegrants are corn starch, soluble starch etc. which have been well dried and powdered. Starches have great affinity for water and swell when moistened thus facilitating the rupture of the tablet matrix, its disintegration action in tablets is due to capillary action. Spherical shape of starch increases the porosity of tablet thus promoting capillary action.

Classification of "Superdisintegrant" may be organized into three classes based on their chemical structure. As shown in Table below.

Table 1: List of Disintegrants

Disintegrants	Concentration in granules (%w/w)	Special comments
Starch USP	5-20	Higher amount is required, poorly compressible
Starch 1500	5-15	-
Avicel®(PH 101, PH 102)	10-20	Lubricant properties and directly compressible
Solka floc®	5-15	Purified wood cellulose
Alginic acid	1-5	Acts by swelling
Na alginate	2.5-10	Acts by swelling
Explotab®	2-8	Sodium starch glycolate, superdisintegrant.
Polyplasdone®(XL)	0.5-5	Cross-linked PVP
Amberlite® (IPR 88)	0.5-5	Ion exchange resin
Methyl cellulose, Na CMC, HPMC	5-10	-
AC-Di-Sol®	1-3	Direct compression
	2-4	Wet granulation

1.5 Incorporation into Immediate Release Dosage Forms[12]

The immediate release dosage form comprises the dispersion, a porosigen, and a disintegrant. The dosage form is in the form of a compressed tablet or other solid dosage form. Other conventional formulation excipients may be employed in the dosage forms including surfactants, pH modifiers, fillers, matrix materials, complexing agents, solubilizers, pigments, lubricants, glidants, flavorants, may be used for customary purposes and in typical amounts without adversely affecting the properties of the compositions.

- **Solid Dispersion:**
  The dosage forms contain a high loading of the solid amorphous dispersion. High loadings of dispersion in the dosage form minimize the size of the dosage form, making it easier for the patient to swallow it and improving patient compliance. Depending on the drug dose, the immediate release dosage form comprises at least 30-50 wt % of the dispersion.This type of dosage forms disintegrates within 10 minutes following introduction to a disintegration medium. The dosage form of the present invention releases at least 70 wt %, more preferably at least 80 wt % and most preferably at least 90 wt % of the low solubility drug within 35 minutes following introduction to a dissolution medium.

- **Concentration-Enhancing Polymers:**
  Concentration enhancing polymers suitable for use in the solid drug dispersions in the sense that they do not chemically react with the drug in an adverse manner. The polymer can be neutral or ionizable, and should have an aqueous solubility of at least 0.1 mg/mL over at least a portion of the pH range of 1-8.
  It is preferred that the concentration-enhancing polymer be "amphiphilic" in nature, meaning that the polymer has hydrophobic and hydrophilic portions. It is believed that such polymers have relatively strong interactions with the drug and may promote the formation of various types of polymer/drug assemblies in solution.
- A particularly preferred class of amphiphilic polymers is those that are ionizable noncellulosic polymers. Exemplary polymers include: carboxylic acid-functionalized vinyl polymers, such as the carboxylic acid-functionalized polymethacrylates and polyacrylates such as the Eudragit; amine-functionalized polyacrylates and polymethacrylates; proteins, such as gelatin and albumin; and carboxylic acidfunctionalized starches such as starch glycolate. Another class of polymers suitable for use comprises non-ionizable or neutral non-cellulosic polymers. Exemplary polymers include: vinyl polymers and copolymers having at least one substituent selected from the group consisting of hydroxyl, alkylacyloxy, and cyclicamido; polyvinyl alcohols; polyvinyl alcohol polyvinyl acetate copolymers; polyvinyl pyrrolidone; polyethylene polyvinyl alcohol copolymers.
- The amount of concentration-enhancing polymer relative to the amount of drug present in the solid drug dispersions depends on the drug and concentration-enhancing polymer and may vary widely from a drug-to-polymer weight ratio of 0.01 to 5, or from about 1 to about 80 wt % drugs. However, in most cases, except when the drug dose is quite low, i.e., 25 mg or less, it is preferred that the drug-to-polymer ratio is greater than 0.05 and less than 2.5. The maximum drug: polymer ratio that yields satisfactory results varies from drug to drug and is best determined in the in vitro and/or in vivo dissolution tests.

- **Preparation of Dispersions:**
  Different methods are also been used for preparation of solid dispersions such as Melting method, Solvent method, Melting solvent method (melt evaporation), Melt extrusion method, Lyophilisation Technique, Melt Agglomeration Process, The Use Of Surfactant, Electrospinning and Super Critical Fluid Technology.

- **Disintegrants:**
  As disintegrants sodium starch glycolate(SSG), sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, Crospovidone, polyvinyl polypyrrolidone, methyl cellulose, microcrystalline cellulose, powdered cellulose, lower alkyl-substituted hydroxypropyl cellulose, polacrilin potassium, starch, pregelatinized starch, sodium alginate, and mixtures thereof. The amount of disintegrant included in the dosage form will depend on several factors, including the properties of the dispersion, the properties of the porosigen and the properties of the disintegrant selected. Generally, the disintegrant will comprise from 1 wt % to 25 wt % of the dosage form.

- **Porosigen:**
  The dosage form also includes a porosigen. A "porosigen" is a material that, when present in the formulation containing the solid amorphous dispersion, leads to a high porosity and high strength following compression of the blend into a tablet. In addition, preferred porosigen are soluble in an acidic environment with aqueous solubility typically greater than 1 mg/mL at a pH less than about 5. Examples of porosigens include acacia, calcium carbonate, calcium sulfate, calcium sulfate dihydrate, compressible sugar, dibasic calcium phosphate, tribasic calcium phosphate, monobasic sodium phosphate, dibasic sodium phosphate, lactose, magnesium oxide, magnesium carbonate, silicon dioxide, magnesium aluminum silicate, maltodextrin, mannitol, methyl cellulose, microcrystalline cellulose, sorbitol, sucrose, xylitol and mixtures thereof. Generally, the porosigen will comprise from 5 to 70 wt %. To ensure the tablet has sufficient porosity to allow adequate wicking of water into the tablet to cause rapid tablet disintegration and/or rapid release of drug, tablet porosity should be within 0.15-0.25. Accordingly, the disintegrant and porosigen should be selected so that the immediate release dosage form has high strength as well as the high porosity required to achieve rapid disintegration and/or release of drug.

- **Surfactants:**
  One very useful class of excipients is surfactants, preferably present from 0 to 10 wt %. Suitable surfactants include fatty acid and alkyl sulfonates; commercial surfactants such as benzalkonium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene sorbitan fatty acid esters, natural surfactants such as sodium taurocholic acid, lecithin, and other phospholipids and mono- and diglycerides; and mixtures thereof. Such materials can advantageously be employed to increase the rate of dissolution by, for example, facilitating wetting, or otherwise increase the rate of drug release from the dosage form.

- **pH Modifiers:**
  Inclusion of pH modifiers such as acids, bases, or buffers may also be beneficial in an amount of from 0 to 10 wt %. Acidic pH modifiers (e.g., acids such as citric acid or succinic acid) retard the dissolution of the pharmaceutical composition when the dispersion polymer is anionic. Alternatively, basic pH modifiers (e.g., sodium acetate or amines) enhance the rate of dissolution of the same types of pharmaceutical composition.

- **Diluents:**
  Examples of other matrix materials, fillers, or diluents include lactose, mannitol, xylitol, dextrose, sucrose, sorbitol, compressible sugar, microcrystalline cellulose, powdered cellulose, starch, pregelatinized starch, dextrates, dextran, dextrin, dextrose, maltodextrin, calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, magnesium carbonate, magnesium oxide, poloxamers, polyethylene oxide, hydroxypropyl methyl cellulose and mixtures thereof.

- **Surface Active Agents:**
  Sodium lauryl sulfate and polysorbate 80. Drug-complexing agents or solubilizers include the polyethylene glycols, caffeine, xanthene, gentisic acid and cylodextrins.

- **Lubricants:**
  Examples of lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

- **Glidants:**
  Examples of glidants include silicon dioxide, talc and cornstarch. Preferably from 10 to 50 wt % of the dosage form Tablets are generally formed by blending the dispersion, disintegrant, and porosigen with optional excipients and then compressing the powder to form tablets. Often it is desirable to granulate the compositions, with or without the addition of excipients prior to compression. For example, the dispersion, disintegrant, and porosigen may be granulated by mechanical means for example, roller compaction or "slugging," followed by milling to form granules. The granules typically have improved flow, handling, blending, and compression properties relative to the ungranulated materials. Wet granulation techniques may also be employed, provided the solvents and process selected do not alter the properties of the solid amorphous dispersion. Improved wetting, disintegrating, dispersing and dissolution properties may be obtained by the inclusion of other excipients.

After the tablet is formed by compression, it is desired that the tablet has "strength" of at least 5-10 Kp/cm2. Here, "strength" is the fracture force, also known as the tablet "hardness," required to fracture a tablet formed from the materials. The fracture force may be measured using a Schleuniger Tablet Hardness Tester. Friability is a wellknown measure of a tablet's resistance to surface abrasion that measures weight loss in percentage after subjecting the tablets to a standardized agitation procedure. Friability values of from 0.8 to 1.0% are regarded as constituting the upper limit of acceptability

1.5 Evaluation of Tablet:

Strategies for Development of Immediate Release Tablets:

The present formulation of immediate release tablet of antihypertensive drug developed by previously taken preliminary batches that give desire in vitro drug release profile comparable to market product all batches were taken by the defined manufacturing process.

1.6 Formula: By Wet Granulation and Direct Compression

Table 1: Formulation of Trial Batches F1 To F10

Batch No.		F1	F2	F3	F4
SR. NO.	INGREDIENTS	mg/tablet wet granulation	mg/tablet DC	mg/tablet DC with 0.5%Aerosil	mg/tablet use mcc102 &reduce conc.with DC
1	DRUG X	10	10	10	10
2	MICROCRYSTALLINE CELLULOSE (Avicel PH 101)	52	52	52	-
3	MICROCRYSTALLINE CELLULOSE (Avicel PH 102)	-	-	-	10
4	POVIDONE K-30	2	2	2	2
5	LACTOSE MONOHYDRATE	130	130	130	172
6	PURIFIED WATER	q.s	-	-	-
17	CROSSPOVIDONE XL-10	4	4	4	4
8	SSF	2.0	2.0	2	2
	TOTAL	200.00	200.0	200.00	200.00

Table 2

Batch No.		F5	F6	F7	F8
Sr. No.	Ingredients	mg/tablet low moisture grade excipients with DC	mg/tablet same as F5 but wet granulation	mg/tablet IPA granulation with maleic acid	mg/tablet IPA granulation
1	DRUG X	10	10	10	10
2	MICROCRYSTALLINE CELLULOSE (Avicel PH 112)	10	10	10	10
3	POVIDONE K-30	2	2	2	2
4	LACTOSE ANHYDROUS.	172.0	170.	170	172
5	MALEIC ACID			2	
6	IPA			q.s	q.s
7	PURIFIED WATER	-	q.s	-	-
8	CROSSPOVIDONE XL-10	4	4	4	4
9	SSF	2.0	2.0	2	2
	TOTAL	200.00	200.0	200.00	200.00

Table 3

Batch No.		F9	F10
SR. NO.	Ingredients	mg/tablet IPA granulation	mg/tablet IPA granulation
1	DRUG X	10	10
2	MICROCRYSTALLINE CELLULOSE (Avicel PH 112)	10	10
3	POVIDONE K-30	2	2
4	LACTOSE ANHYDROUS.	172.0	172
6	IPA	q.s	q.s
8	CROSSPOVIDONE XL-10	4	4
9	SSF	2.0	2
	TOTAL	200.00	200.00

1.7 Procedure for Wet Granulation:

○ **STEP I:**

- Dispensing of Drug and Excipients.

○ **STEP II:**

- Sifting and Mixing
- Sift through sieve no. 30
- Dry mixing in RMG (rapid mixer granulator) for 10 minutes.
- Calculate Bulk density of dry mix.

○ **STEP III:**

- Granulation
- Binder solution : water and IPA
- Binder addition: using slow impeller in RMG

○ **STEP IV:**

- Drying
- In FBD (Fluidised bed dryer) at 55°C - 60°C.

○ **STEP V:**

- Sizing
- In oscillator granulator through sieve no. 20.
- Calculation of LOD (loss on drying) in halogen moisture analyser.
- Calculation of bulk density, tapped density, angle of repose, compressibility index and yield.

○ **STEP VI:**

- Blending and Lubrication

○ **STEP VII:**

- Compression
- B tooling 16 station machine.
- Parameters to be controlled: weight of tablet, hardness, thickness, diameter, friability and disintegration time.

1.8 Procedure Dry Granulation:

○ **STEP I:**

- Dispensing of Drug and Excipients.

○ **STEP II:**

- Sifting and Mixing
- Sift through sieve no. 30 and SSF through sieve no. 60.

- Calculate Bulk density of dry mix.

○ **STEP I1I:**

- Sizing
- Calculation of LOD (loss on drying) in halogen moisture analyser.
- Calculation of bulk density, tapped density, angle of repose, compressibility index and yield.

○ **STEP IV :**

- Blending and Lubrication

○ **STEP V:**

- Compression
- B tooling 16 station machine.
- Parameters to be controlled: weight of tablet, hardness, thickness, diameter, friability and disintegration time.

Note:

- **Batch F1** carried out by wet granulation with water but impurity is very high compare to USP limit as NMT 4.0%and also drug release problems accurse.
- **Batch F2** carried out by direct compression but result in very poor flow and also sticking problems with die.and impurity is reduced with compare batch f1.
- **Batch F3** this batch carried out by direct compression with 0.5% aerosol for poor flow of batch f2 but not this problem is solved by aerosol.
- **Batch F4** carried out by direct compression with changing mcc 101 garde to mcc 102 and reduced conc. Of mcc 102, resulting in impurity is very lower compare to other batch but not less than 4%. As mcc increasess, increase in impurity is observed.
- **Batch F5** carried out by direct compression with using low moisture grade mcc 112 and redused conc. Of mcc 112 resulting impurity is lower compare to batch f4 but flow problem is not solved.
- **Batch F6** carried out same as f5 but wet granulation with water, batch f1 also carried out by wet granulation with water but f6 in this batch mcc 112 use and resulting impurity is lowerd 40% but not less than 4.0% as per USP limit .and flow problem is solved.
- **Batch F7** carried out by wet granulation with IPA and also add maleic acid for stabilizing malate salat of anarprile but not stability problem is solved and impurity problem also accurse.
- **Batch F8** carried out by wet granulation with IPA and not add maleic acid,ans last stability study at **40/75**% RH. For 2 month impurity is 1.40 % is observed.and innovator impurity at **40/75**% RH for 2 month impurity is 2.90 %.
- **Batch F9&F10** is optimization of batch f8 and also drug release profile ,DT, Hardness ,etc match with inovetor product of Bristol-Mayer Squibb ,brazil.

1.9 Evaluation of Tablets[41,]

Immediate release tablets were evaluated for the following parameters.

a) Physical characterization
- Hardness.
- Disintegration time
- Thickness.
- Friability.
- Weight variation.

b). Assay

c). Related substances

d). Dissolution (*In-Vitro* release).

a). Physical characterization:

- **Appearance:** The general appearance and elegance of tablet was identified visually, which include tablet size, shape, color, presence or absence of an odor, taste, surface texture avoid of sticking etc.
- **Hardness:** Tablets require certain amount of strength or hardness and resistance to friability, to with stand mechanical shocks of handling in manufacture, packaging, and shipping. The most widely used apparatus to measure tablet hardness (crushing strength) is the Schleuniger hardness tester.
- **Method:** Ten tablets were randomly selected and hardness was measured in Schleuniger

hardness tester. The average was taken as hardness of the tablet.

- **Friability:** Friability is related to tablets ability to withstand both shocks and abrasion without crumbling during manufacturing, packing, transportation and consumer handling. Friability can be evaluated by means of friability test apparatus. Compressed tablets that loose less than 0.5% to 1.0% w/w are generally considered acceptable.
- **Method:** accurately weighed 6.5 gm of tablet and transfer into Friabilator and subjected to 100 revolutions in 4 minutes. Dedusted tablets were reweighed (final wt). Friability was calculated as below formula.

$$\% \text{ Friability} = \frac{(\text{Initial Weight} - \text{final weight})}{(\text{Initial weight})} \text{ X } 100$$

- **Thickness:** Ten Tablets were selected at random from individual formulations and thickness was measured by using vernier caliper scale, which permits accurate measurement.
- **Weight variation:** Twenty tablets were taken randomly, weigh individually and average weight was determined. The individual tablet weight was compared with average tablet weight.

Table 6.17: Weight variation for uncoated tablets

Avg. Weight	Maximum % difference allowed
< 80	10
80-324	7.5
> 324	5

2. Result and Disscusion:

Comparative Dissolution Profile of F1 To F9 in Water

2.1 Wet Granulation &Direct Compression Results

Bulk Properties:

Table 1: Bulk Properties Result

Batch	Bulk Density	Tapped Density	Angle Of Repose	% Compressibility	Loss On Drying
F8	0.665	O.865	28.20	23.12	2.54
F9	0.635	0.834	29.21	23.86	2.67
F10	0.640	0.870	28.45	26.43	2.75

2.2 Compression Parameters:

Table 2: Compression Parameters Result

Batch	Weight (Mg)	Hardness (Kps)	Thickness (Mm)	Disintegration Time (Minutes)	Friability (%)
F8	198 To 202	9.2 To 14.5	4.02	4-5 Minutes	Less Than 1%
F9	200 To 203	8.3 To 14.2	4.04	4-5 Minutes	Less Than 1%
F10	200 To 203	8.5 To 14.8	4.02	4-5 Minutes	Less Than 1%

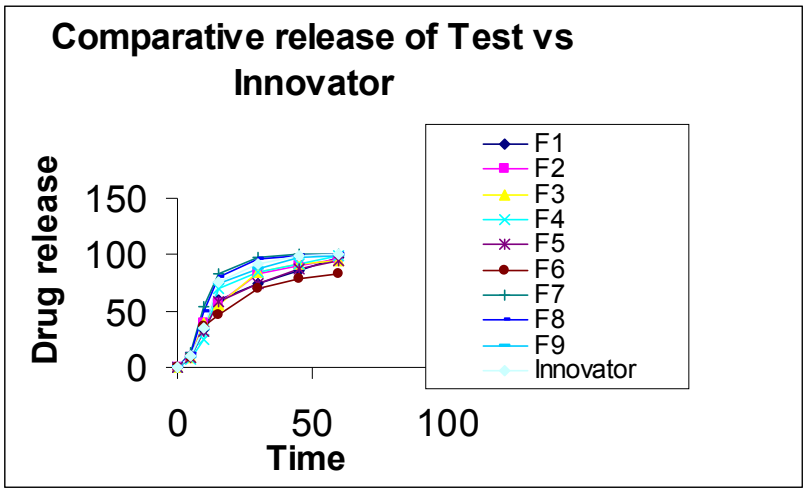
2.3 Dissolution Test:

1. Compared to that of innovator drug product.
Medium - Dissolution in 900ml, water
Appratus – Paddle at 50 rpm

Table .3

Time	WATER % Mean Dissolution At Different Time Interval
In	Olmesartan Medoxomile

Minute	F2	F3	F4	F5	F6	F7	F8	F9	F10	Innovator
0	0	0	0	0	0	0	0	0	0	**0**
5	33.6	60.2	68.2	71.1	70.7	61.6	54	55.3	54.3	**49.8**
10	60.4	95.4	98.3	101.6	96.2	91.3	87.2	89.1	88.4	**90.7**
15	81.5	98.5	100.2	104.5	102.5	96.7	95.0	98.2	98.2	**98.9**
30	92.1	98.5	100.5	104.8	103.9	98.1	98.1	99.8	99.4	**100.1**
45	94.3	98.3	101.3	104.2	103.7	98.6	99.8	100.0	100.2	**101.3**
60	97.3	98.1	101.8	104.3	104.2	99.4	100.0	100.7	100.6	**101.2**



3. Summary and Conclusion

The aim of dissertation entitled "Design, Development and Characterization of immediate release tablet containing antihypertensive drug" was to formulate a stable as well as robust dosage form.

The basic objective was to develop a generic version of antihypertensive tablets in line with the innovator. A generic version of Tablets was developed that is safe, efficacious and bioequivalent to the reference product.

Blend ready for compression was evaluated for bulk density, tapped density, Carr's index and Hausner's Ratio. It was found that blend had Carr's index from 11% to 15% and Hausner's Ratio from 1.12 to 1.18, which indicate that ready for compression blend was good flow property and compressibility property.

The formulation of immediate release tablet was done by direct compression, wet granulation by RMG. From all of these formulation technique direct compression was not effective method but wet granulation by IPA shows improve stability and drug release profile that was in line with innovator.

Total ten formulations were prepared using different grade of microcrystaline cellulose and lactose mono hydrate in different ratios along with lubricant and diluent. The tablets were evaluated for thickness, disintegration, hardness, friability, drug release, wt. variation and assay. The thickness of the tablet varied from 4.02 ± 0.05 mm. The disintegrating time was found to be between 4 min to 5 min . The hardness was in range of 8-15 Kp. Assay for different batches were found to be varied from 98.2 ± 0.5 to 101.7 ± 0.5 indicating the uniformity in drug content within tablets.

All nine formulations were evaluated for *in vitro* drug release in water, over a period of 2-3 hours

using USP type II dissolution apparatus at 50 rpm. The dissolution profiles of the batches were compared with that of innovator product. Among all ten formulations F8, F9 F10 batch showed matching *in vitro* drug release to that of innovator. Batch F1 to F10 was charged for stability. After 2 months of accelerated study, samples were withdrawn and tablet showed no change physical appearances, assay, drug release which indicate that the tablet was stable.

Immediate release tablets formulated by wet granulation showed comparable result with innovator. The techniques employed were practically simple and commercial exploited. From the results it can be concluded that batch F8, F9,F10 showed matching result with innovator. Hence antihypertensive Drug-X and can be successfully formulated as an immediate release tablet.

References

1. Aulton ME. "Pharmaceutics" The Science of dosage form design; 2nd Ed. Churchill livingstone. 2002: 398, 365-374, 414-418.
2. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. Tablets; 3rd Ed. Varghese publishing house, Bombay. 1987:294, 336, 413.
3. Lieberman HA, Lachman L, Schwartz JB. Pharmaceutical Dosage Forms: Tablets, Marcel Dekker Inc, New York. Vol 1,2nd Ed: 195-229.
4. Basic consideration of tablets. Available from [cited on 2011 Mar 17] URL: http://en.wikipedia.org/wiki/Tablet
5. Melkebeke BV, Vervaet C, Remon JP. Validation of a continuous granulation process using a twin-screw extruder. Inter. J of Pharm. 2008; 356:224-230.
6. Swarbrick J. Encyclopedia of Pharmaceutical Technology. Informa Healthcare USA, Inc., New York. 3rd Ed: 3641, 3657-59, 3612-13, 3928.
7. Granulation Techniques, Drying process in tablet manufacturing. [cited on 2011 Mar 22] Available from URL: http://www.pharmapedia.com.
8. Allen LV, Popovich NG, Ansel HC. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Lippincott Williams and Wilkins, Baltimore USA. 8th Ed. 2006:239-244.
9. Jorgensen AC. Increasing process understanding of wet granulation by spectroscopic methods and dimension reduction tools. Faculty of Pharmacy of the University of Helsinki. Oct 2004.
10. Parikh DM. Theory of Granulation, Handbook of Pharmaceutical Granulation Technology. 2nd Ed. 2005:7-33.
11. Chien YW. Novel drug delivery systems. Marcel Dekker Inc. 2nd Ed. 1992:139-40.
12. Leah E, Appel DT, Friesen JE, Byers MD, Crew BC, Hancock SJ, Schadtle. Immediate release dosage forms containing solid drug dispersion. United States Patent No. 424465; 2002.
13. US-FDA guideline.
14. Castell D. Review of immediate-release omeprazole for the treatment of gastric acid-related disorders,1998
15. Krause J, Thommes M, Breitkreutz J. *et al*., Immediate release pellets with lipid binders obtained by solvent-free cold extrusion., *Eu. J. Pharm.* and Bio. 2009, 71,138-144.
16. Parikh BN, Patel DM, Patel CN, Dave JB, Gothi GD, Patel TD. *et al*., Formulation, Optimization And Evaluation Of Immediate Release Tablet Of Telmisartan., *J. Glo. Pharm. Tec.*, www.jgpt.co.in, ISSN:-0975-8542.
17. Rao MR, Bachha VD, Goga DV. , Formulation and evaluation of aceclofenac immediate release tablets. 2007;6: (61), 73-78.
18. Ria VK, Pathak N, Bhaskar R, Nandi BC, Dey S *et al.* Optimization of immediate release tablet of Raloxifene Hydrochloride by wet granulation method. *Inter. J. pharma. Sci and Drug Res.*, 2009; 1(1): 51-54.
19. Shiyani B, Gattani S, Surana S., Formulation and evaluation of bi-layer tablet of metoclopramide hydrochloride and ibuprofen. Available from: http://www.Pub med.gov
20. Jain *et al*., Formulated and evaluated immediate release tablet of Nimesulide Tablets, Int. Symp. Cntr. Rel. Bioact. Mater. 1988 ;15: 101-102.
21. Gupta A, Hunt RL, Shah RB, Sayeed VA, *et al*, Disintegration of highly soluble immediate release tablets: A surrogate for dissolution *AAPS Pharm. Sci. Tech.* 2009.
22. Dumont ML, Berry MR, Nickerson B, probability of passing dissolution acceptance criteria for an immediate release tablets, *J. of Pharm. and Bio. Ana.* 2007; 44: 79-84.
23. Margret CR, Jayakar B, Pasupathi A, Chakrabarty BL, Maurya. P, design development and evaluation of immediate release atorvastatin and sustained release gliclazide tablets, *J. of Pharm.* Res. 2009; 2(6): 1039-1041.
24. Shao Q, Rowe RC, York P, comparison of neurofazzy logic and neural networks in modeling experimental data of an immediate

release tablets formulation, *Eur. J. Pharm. Sci*. 2006; 28: 394-404.
25. Souliman S, Blanquet S, Beyssac E, Cardot MJ, A level A in *in vivo/in vitro* correlation in fasted and fed states using different methods applied to solid immediate release oral dosage form, *Eur. J. Pharm. Sci*. 2006;27: 72-79.
26. Dukic´-Ott A, Remon JP, Foreman P, Vervaet C, Immediate release of poorly soluble drugs from starch-based pellets prepared via extrusion/spheronization, *Eur. J. Pharm. and Biopharm*. 2007; 67: 715–724.
27. Schreiner T, Schaefer UF, Loth H, Immediate Drug Release from Solid Oral Dosage Forms, *J. of Pharm. Sci.*, 2005; 94(1): 120-133.
28. Shiyani BG, Dholakiya RB, Akbari BV, Lodhiya DJ, Ramani GK,. Development and evaluation of novel immediate release tablets of Metoclopramide HCl by direct compression using treated gellan gum as a disintegration-accelerating agent. *J. of Pharm.* Res.2009;2(9): 1460-64.
29. Gupta E, Barends DM, Yamashita E, Lentz KA, *et al*, review on global regulation concerning biowaviers for immediate release solid oral dosage forms *Eur. J. pharm. Sci*., 2006; 29(3-4): 315-324.Monograph of Anti-Diabetic Agent, Takeda Canada, Inc, 2009.
30. Chaplin G, Pugsley T, Winters C, monitoring the fluidized bed granulation process based on S-Statistical analysis of pressure time series, *AAPS Pharm. Sci. Tec.*, 2005; 6(2): E198-201.
31. Goldschmidt M.J.V., Weijers G.G.C., Boerefijn R., Kuipers J.A.M, discrete element modeling of fluidized bed spraygranulation.
32. Krause J, Thommes M, Breitkreutz J, Immediate release pellets with lipid binders obtained by solvent-free cold extrusion, *Eur. J. Pharm. and Biopharm*. 2009; 71: 138–144.
33. [cited 2011 Mar 15] http://www.rxlist.com/script/main/srchcont_rxlist.asp?src=losartan+hctz&x=0&y=0.
34. Material safety data sheet of lactose monohydrate, [cited 2011 Apr 12]. Available from URL:http://www.sciencelab.com.
35. Lactose monohydrate, [cited 2011 Apr 12]. Available from URL: http://www.chemblink.com
36. Rowe RC, Sheskey PJ, Handbook of pharmaceutical excipients, 5th ed, 2006 .
37. Hydroxypropyl cellulose: klucel product data, [cited 2011 Apr 12]. Available from URL: http://www.signetchem.com.
38. Nisso HPC SSL, [cited 2011 Apr 12].Available from URL:http://www.nissoamerica.com.
39. Monograph of magnesium Stearate, [cited 2011 Apr 12]. Available from URL: http://www.lohmann-chemikalien.de.
40. Handbook of pharmaceutical excipient page no:-108,289,297,323,354,609
41. European Pharmacopoeia, page no 1299-1300.
42. Lachman L, Lieberman HA, Kanig JL. The theory and practice of Industrial pharmacy, Varghese Publishing House Bombay; 1987:171-293.