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IN-VITRO CHARACTERIZATION DESIGN DEVELOPMENT AND METOLAZONE IMMEDIATE RELEASE TABLETS

Cheguri Sravani[1]*, Dr. Purushothaman M[2]

[1]Student, Department of Pharmaceutics, KLR Pharmacy College, Palwancha, Telangana 507115, India.
[2]Principal, Department of Pharmaceutics, KLR Pharmacy College, Palwancha, Telangana 507115, India.

ABSTRACT
Metolazone is a thiazide-like diuretic. It is primarily used to treat congestive heart failure and high blood pressure. Metolazone indirectly decreases the amount of water reabsorbed into the bloodstream by the kidney, so that blood volume decreases and urine volume increases. This lowers blood pressure and prevents excess fluid accumulation in heart failure. Metolazone is sometimes used together with loop diuretics such as furosemide or bumetanide, but these highly effective combinations can lead to dehydration and electrolyte abnormalities. In the present work, an attempt has been made to develop Immediate release tablets of Metolazone. Cross povidone, Aegle Marmelos Bael (Gum) and Locust bean gum were employed as super disintegrating agents to enhance the solubility and dissolution rate of selected drug molecule. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F1 formulation showed maximum % drug release i.e., 97.62 % in 25 min hence it is considered as optimized formulation. The F1 formulation contains cross povidone as super disintegrate in the concentration of 5 mg.

Key Words: Metolazone, Cross povidone, Aegle Marmelos Bael (Gum) and Locust bean gum

INTRODUCTION

Immediate release tablets remain solid till administration and possess dose accuracy and stability during storage which transform into liquid form within few seconds after its administration for easy swallowing [1]. Immediate release tablets have significant advantages of both solid and liquid dosage forms Advantages of this drug delivery system include administration without water, convenience of administration and accurate dosing as compare to liquids, easy portability, ability to provide advantages of liquid medication in the form of solid preparation, ideal for pediatric and geriatric patients and rapid dissolution/absorption of the drug, which may produce rapid onset of action [2].

Corresponding Author
Cheguri Sravani

Email: sravanicheguri75696@gmail.com

Advantages of Immediate Release Drug Delivery System

- An immediate release pharmaceutical preparation offers
- Improved compliance/added convenience
- Improved stability
- Suitable for controlled/sustained release actives
- Allows high drug loading.

Disadvantage:

- Frequent dosing is necessary for a drug with a short half-life.
- Drug release at a time may produce high plasma concentration which may produce toxicity [3].

Difficulties with Existing Oral Dosage Form

- ✓ Patient may suffer from tremors therefore they have difficulty to take powder and liquids.
- ✓ Swallowing of solid dosage forms like tablet and capsules and produce difficulty for young

- ✓ adult of incomplete development of muscular and nervous system and elderly patients suffer from dysphasia [4].
- ✓ Cost of products is main factor as parenteral formulations are most costly and discomfort.

Tablet Manufacturing

The manufacturing of oral solid dosage forms such as tablets is a complex multi-stage process under which the starting materials change their physical characteristics a number of times before the final dosage form is produced [5]. Traditionally, tablets have been made by granulation. Both wet granulation and dry granulation or direct compression is used.

Desired Criteria for Immediate Release Drug Delivery System

Immediate release dosage form should- In the case of solid dosage it should dissolve or disintegrate in the stomach within a short period.

1. In the case of liquid dosage form it should be compatible with taste masking.
2. Be portable without fragility concern.
3. Have a pleasing mouth feel.
4. It should not leave minimal or no residue in the mouth after oral administration.
5. Exhibit low sensitivity to environmental condition as humidity and temperature.
6. Be manufactured using conventional processing and packaging equipment at low cost.
7. Rapid dissolution and absorption of drug, which may produce rapid onset of action.

Conventional Techniques Used for Preparation of Immediate Release Tablets:

Several technologies are available to manufacture immediate-release tablets. The most common preparation methods are molding, lyophilization or freeze drying, direct compression, spray drying and sublimation [6].

Tablet Molding Technique:

In this technology, water-soluble ingredients are incorporated to disintegrate and dissolve the tablet more swiftly. The hydroalcoholic solvents are used to moistened powder blend and then apply compression pressure that is lower than the conventional tablets compression to mold the tablet.

Direct Compression:

In which tablets formulations are directly compressed from a powder blend of suitable excipients and API is called a direct compression method. Pre-treatment of blended powder by dry or wet granulation procedure is not necessary. It provides merits mostly in terms of speedy production, as it requires less machinery, reduced number of personnel, fewer unit operations and significantly less processing time along with improved product stability.

Granulation Technique:

It is a process of size enlargement in which small particles convert into larger agglomerates and make it physically stronger. It is beneficial to avoid segregation of the product's constituent, refine powder flow and handling and minimize the dustiness.

Wet Granulation:

Wet granulation process make easy fine particles run into severity-feed drug manufacturing. Usually, immediate release formulation is granulated with addition into fine particles accumulation an aqueous solution of a binding polymer. Controlled release formulation granulated with addition a binder polymer solution

Dry Granulation:

In dry granulation process the powder mixture is compressed without the use of heat and solvent. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain granules. Below two methods are used for dry granulation [7, 8].

Mass-Extrusion:

In this technology softening the blend of active drug with water-soluble solvent methanol, polyethylene glycol and softened mass put into the extruder to form a cylinder shape of the product and segmented with using the heated blade to formulate a dosage form as tablets [9].

Solid Dispersions:

Solid products containing at least two different components, mainly hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. This method deal with the challenge of mixing a matrix and drug, preferably on a molecular level, while matrix and drug are generally poorly miscible 19. When formulating immediate release solid dosage forms from solid amorphous dispersion for oral administration to effective use in an environment such as the GI tract of a human, it is often desirable to increase the amount of dispersion occurs in the dosage form [10].

Novel Granulation Technologies:

- ✓ Pneumatic Dry Granulation (PDG):
- ✓ Freeze Granulation Technology (FGT):
- ✓ Spray Drying Granulation:
- ✓ TOPO (TOPO Granulator) Technology:
- ✓ Moisture Activated Dry Granulation (MADG):
- ✓ Continuous Flow Technology:
- ✓ Thermal Adhesion Granulation Process:
- ✓ Granurex Technology:
- ✓ Foamed Binder Technologies:

Superdisintegrants:

Disintegrants are substances or a mixture of substances incorporated to the drug formulations, which assist dispersion or breakup of tablets and contents of capsules into smaller fragments for rapid dissolution.

Swelling:

The most commonly accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show weak disintegration due to lack of adequate swelling force. On the flip side, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is not able to penetrate in the tablet and disintegration is again slows down [11].

Capillary Action / Wicking:

Those disintegrating agents do not get swells so they acted by the mechanism of capillary action and porosity [12]. Tablet's porosity provides a direction to penetrate the fluid into the dosage form. The disintegrating particles those having low compressibility and cohesiveness they facilitate the high porosity and provide a pathway to wicked and drawn up liquid in the tablets drawn through capillary action and break the bonding of inter particles which leads the tablet to break apart.

Chemical Reaction (Acid-Base Reaction):

The tablet is quickly ruptured apart by the internal release of CO2 in water due to the interaction between tartaric acid and citric acid (acids) with alkali metal carbonates or bicarbonates (bases) in the presence of water. Due to the generation of pressure tablet disintegrates. The dissolution of API in water and taste masking influence due to liberation in CO2 gas. During preparation of the tablets, the strict control environment is necessitated for these disintegrants are highly sensitive to small change in humidity level and temperature. The effervescent blend is either added instantly before compression or can be added in two discrete fractions of formulation.

Deformation:

The elastic nature of starch grains are easily deformed under pressure and return to their native position and shape when the pressure is removed. But when compression forces are applied to the tableting process, these grains are get deformed permanently and called as "energy-rich" and this is energy released while come to contact with water.

Particle Repulsive Forces Due to Disintegrating Particle:

According to Guyot-Hermann's particle repulsion theory, water penetrates tablet via hydrophilic pores, and persistently starch network is fabricated that can transfer water from one particle to the next, imparting a significant hydrostatic pressure. Water is necessary for this mechanism of disintegration by repulsive electric forces between particles.

Enzymatic-Reaction:

Enzymes also act as disintegrants that are present in the body. These enzymes have a deficiency of binding action of binder and assist in disintegration. Due to swelling, the pressure is applied in the outer direction that the reason for the tablet to burst or the accelerated absorption of water leads to a vast increase in the volume of granules to stimulate disintegration [13].

MATERIALS

Metolazone, Microcrystalline cellulose, Crospovidone, Locust bean gum, Aegle Marmelos Bael(Gum), Magnesium stearate, Talc.

METHODOLOGY

Preformulation Studies

The goals of the preformulation study are:

- To establish the necessary physicochemical characteristics of a new drug substance.
- To determine its kinetic release rate profile.
- To establish its compatibility with different excipients.

Hence, preformulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies and flow properties.

Determination of absorption maximum (λ_{max}):

Absorption maximum is the wavelength at which maximum absorption takes place. For accurate analytical work, it is important to determine the absorption maxima of the substance under study. Metolazone was weighed accurately 10 mg and transferred to 100 ml volumetric flask, dissolved in phosphate buffer pH 6.8 and the final volume was made up to 100 ml with phosphate buffer pH 6.8 to get a stock solution (100µg/ml). From the stock solution, 1 ml was pipette out in 10 ml volumetric flask and the final volume was made up to 10 ml with phosphate buffer PH 6.8 to get 10µg/ml. Then this solution was scanned at 200-400nm in UV-Visible double beam spectrophotometer (UV-3200, Labindia, India) to get the absorption maximum (λ_{max}).

Construction of Metolazone calibration curve with phosphate buffer pH 6.8:

100mg of Metolazone was dissolved in 100ml of phosphate buffer pH 6.8 to give a concentration of 1mg/ml (1000µgm/ml). From the above standard solution (1000µgm/ml) 10 ml was taken and diluted to 100ml with phosphate buffer pH 6.8 to give a concentration of 100µgm/ml. From this stock solution aliquots of 0.2,0.4,0.6,0.8, and 1 ml were pipette out in 10ml volumetric flask and the volume was made up to the mark

with phosphate buffer PH 6.8 to produce concentration of 2,4,6,8 and 10 µgm/ml respectively. The absorbance (abs) of each conc. was measured at respective (λ_{max}) i.e., 220 nm.

Drug- excipient compatibility studies by FT-IR:

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR. The potassium bromide pellets were prepared on KBr press by grounding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless-steel die and was compressed between polished steel anvils at a pressure of about 8t/in^2. The spectra were recorded over the wave number of 8000 to 400cm^{-1}.

Flow properties:

Angle of Repose:

It is performed to determine the flow rate of powder done by the funnel method. The powder was poured into a funnel which is fixed from height of 2cm of the plane surface. Circumference was drawn with a pencil on the graph paper and the radius of base of a pile was measured at 5 different points and average was taken for calculating Angle of repose using following formula:
$\Theta = \tan^{-1} H/R$
Θ=angle of repose, H=height of powder cone, R=radius of powder cone.

Loose bulk Density (LBD):

Loose bulk density was obtained by dividing the mass of powder by the bulk volume in cm^3. The sample of about 50 cm^3 of powder, previously been passed through a standard sieve no. 20, was carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped at 2 second intervals on to hard wood surface three times from a height of 1 inch. The bulk density of each formulation was then obtained by dividing the weight of sample in grams by the final volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below: Df = M /Vp
Df = bulk density, M = weight of sample in grams, Vp = final volume of powder in cm^3

Tapped density (TD):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times if the difference between these two volumes is less than 2%. If it is more than 2%, tapping was continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by
Do = M /Vp
Do = Tapped density, M = weight of sample in grams, Vp = final volume of powder after tapping in cm^3

Carr's consolidation index:

The Carr index is an indication of the compressibility of a powder. This is calculated by the formula

$$C = \frac{(\rho b - \rho t)}{\rho b} \times 100$$

ρ_b is the bulk density, ρ_t is the tapped bulk density

A Carr index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

Hausner's ratio:

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. The Hausner ratio is calculated by the formula

$$H = \rho_{b/} \rho_b$$

ρ_b is the bulk density, ρ_b is the tapped bulk density

Hausner ratio greater than 1.25 is considered to be an indication of poor flowability.

Formulation of Immediate release tablets of Metolazone:

Preparation of tablets:

Composition of Metolazone Immediate release Tablet by direct compression. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 6mm flat punch, B tooling. Each tablet contains 10 mg Metolazone and other pharmaceutical ingredients. Total weight of tablet was found to be 60 mg.

Table 1: Composition of various tablet formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metolazone (mg)	10	10	10	10	10	10	10	10	10
Crospovidone	5	10	15	-	-	-	-	-	-
Aegle Marmelos Bael(Gum)	-	-	-	5	10	15	-	-	-
Locust bean gum	-	-	-	-	-	-	5	10	15
Magnesium Stearate(mg)	3	3	3	3	3	3	3	3	3
Talc(mg)	3	3	3	3	3	3	3	3	3
MCC (mg)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total wt(mg)	60	60	60	60	60	60	60	60	60

Post Compression Parameters:

Evaluation of tablets:

Shape and colour:

The tablets were examined under a lens for the shape of the tablet and colour by keeping the tablets in light.

Uniformity of thickness:

Randomly 10 tablets were taken from formulation batch and their thickness (mm) was measured using a Vernier callipers.

Hardness test:

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Six tablets were randomly picked from each formulation.

Friability test:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche friabilator (Lab India, FT 1020). It is expressed in percentage (%). Ten tablets were initially weighed [$W_{(initial)}$] and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again [$W_{(final)}$]. The percentage friability was then calculated by,

$$F = \frac{[W(initial) - W(final)]}{W(initial)} \times 100$$

Weight variation test:

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The % deviation in weight variation is shown in table.

Drug Content estimation:

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch.

Four tablets were weighed and crushed in the mortar. The powder equivalent to 1.25 mg of the drug were weighed and dissolved in 100ml phosphate buffer pH 6.8 to give a concentration of 12.5 µg/ml. 2ml of this solution was taken and diluted to 10ml to give a concentration of 2.5µg/ml. The absorbance of the prepared solution was measured at 220nm using UV Visible spectrophotometer (Lab India, UV-3200).

***In -vitro* dissolution studies:**

In-vitro release studies were carried out using a modified USP XXIII dissolution test apparatus (Lab India, DS-800). The dissolution fluid was 500ml of phosphate buffer pH 6.8 at a speed of 50rpm at a temperature of 37^0c were used in each test. Samples of dissolution medium (5ml) were withdrawn for every 2min and assayed for Metolazone by measuring absorbance at 220 nm. For all the tests 5ml of the test medium were collected at specified time intervals and replaced with same volume of phosphate buffer pH 6.8 [14, 15, 16].

RESULTS AND DISCUSSION

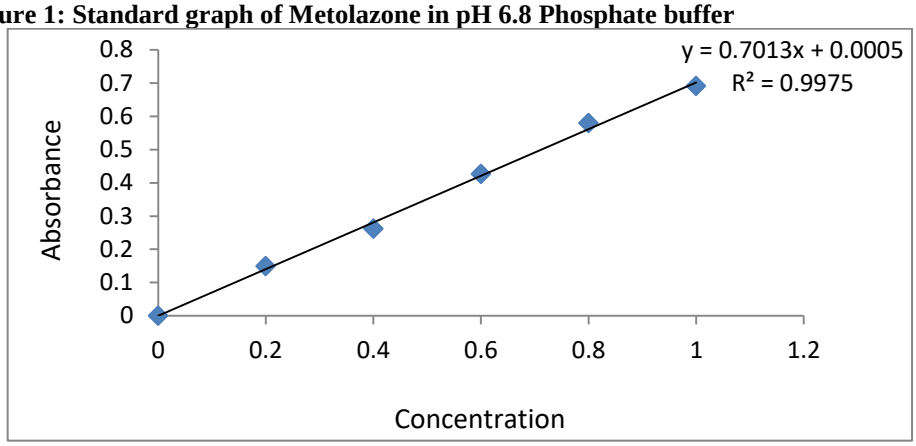
Standard Calibration curve of Metolazone:

Table 2: concentration and absorbance obtained for calibration curve of metolazone in pH 6.8 Phosphate buffer

S. No.	Concentration (µg/ml)	Absorbance (at 220 nm)
1	0	0
2	0.2	0.149
3	0.4	0.262
4	0.6	0.426
5	0.8	0.579
6	1	0.691

It was found that the estimation of Metolazone by UV spectrophotometric method at λ_{max} 220 nm in pH 6.8 Phosphate buffer had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 1- 6µg/ml. The regression equation generated was $y = 0.7013x - 0.0005$, $R^2 = 0.998$.

Figure 1: Standard graph of Metolazone in pH 6.8 Phosphate buffer



Evaluation Parameters for Sublingual Tablets of Metolazone:

FTIR

Figure 2: FTIR Spectrum of pure drug

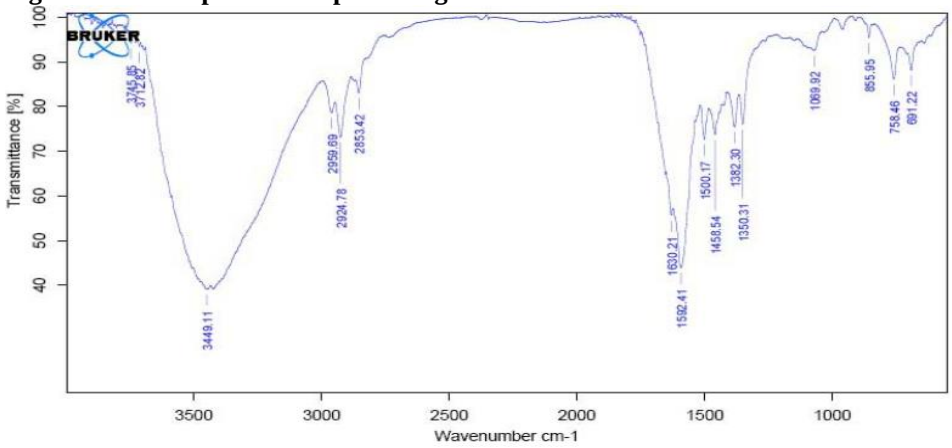
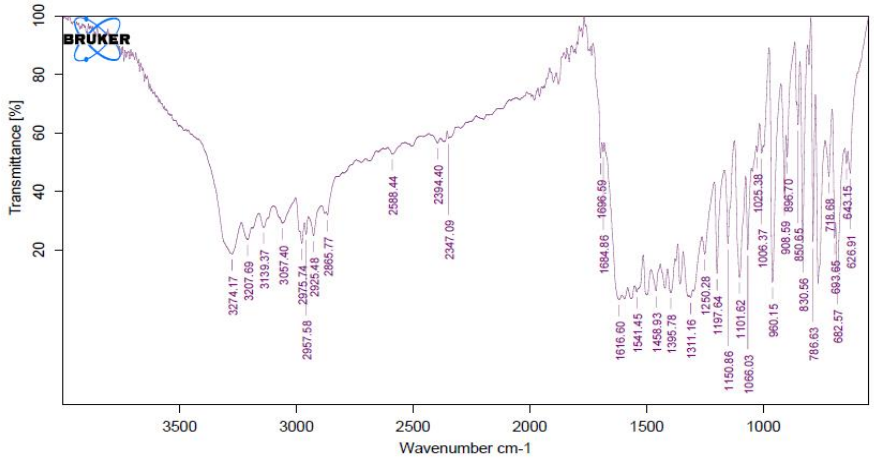


Figure 3: FTIR spectrum of optimized formulation



Pre-compression parameters:

The values for angle of repose were found in the range of 24°-29°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.43 to 0.50 (gm/cc) and 0.50 to 0.59 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 15.01% to 18.01%. The Hausner ration fall in range of 1.04 to 1.31. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.'

Table 3: Pre-compression parameters

Formulations	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner ratio	Angle of Repose(Ɵ)
F1	0.46	0.50	15.71	1.04	24.92
F2	0.47	0.58	16.72	1.29	26.18
F3	0.48	0.53	17.07	1.21	24.86
F4	0.50	0.55	15.01	1.14	25.15
F5	0.46	0.57	16.23	1.17	27.53
F6	0.47	0.59	17.12	1.19	27.14
F7	0.49	0.54	18.01	1.27	24.08
F8	0.44	0.52	16.12	1.29	27.09
F9	0.43	0.58	15.12	1.31	28.07

Post compression Parameters:

Table 4: Post-Compression parameters

Formulation code	Weight variation(mg)	Hardness (kg/cm^2)	Thickness (mm)	Disintegration Time (sec)	Friability(%)	Assay (%)
F1	59	2.2	1.16	57	0.51	96.13
F2	61	2.4	1.15	70	0.54	99.04
F3	60	2.5	1.18	63	0.55	98.82
F4	58	2.4	1.24	64	0.58	99.16
F5	63	2.7	1.17	66	0.57	97.24
F6	64	2.3	1.23	68	0.56	99.58
F7	62	2.4	1.14	69	0.50	97.22
F8	58	2.2	1.22	60	0.53	98.02
F9	63	2.6	1.20	63	0.59	98.99

Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 8.3. The average weight of the tablet is approximately in range of 59 to 63mg, so the permissible limit is ±10% (=60mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test:

Hardness of the three tablets of each batch was checked by using Monsanto hardness tester and the data's were shown in Table 8.3. The results showed that the hardness of the tablets is in range of 2.2 to 2.7 kg/cm^2, which was within IP limits.

Thickness:

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table-4. The result showed that thickness of the tablet is raging from 1.14 to 1.24.

Friability:

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 8.3. The average friability of all the formulations lies in the range of 0.50 to 0.59% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

In vitro disintegration time:

Tablets of each batch were evaluated for in vitro disintegration time and the data were shown in the Table 4. The results showed that the disintegration time of prepared tablets were in the range of 57 to 70 seconds.

Assay:

Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 96.13-99.59%.

Invitro Dissolution studies:

Invitro dissolution studies were carried out by using 500ml of pH 6.8 Phosphate buffer in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 25 min.

Figure 4: Dissolution profile of formulations prepared with Crospovidone as super disintegrate

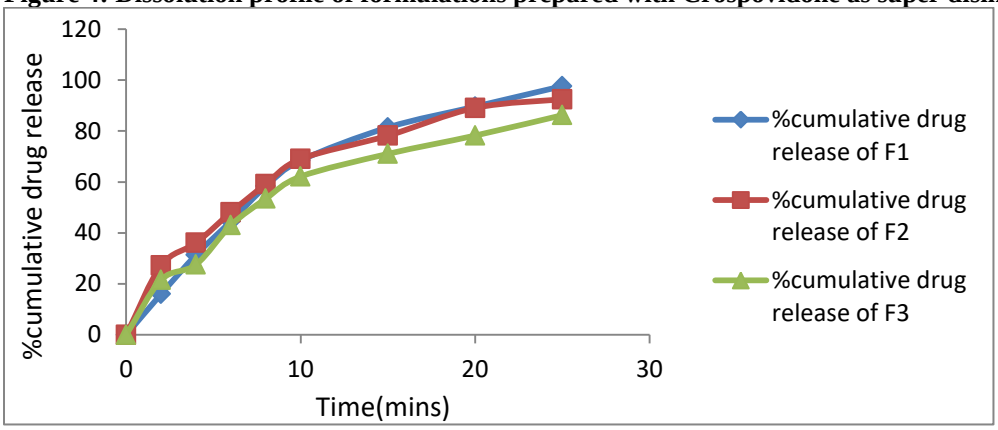


Figure 5: Dissolution profile of formulations prepared with Aegle Marmelos Bael(Gum) as super disintegrate

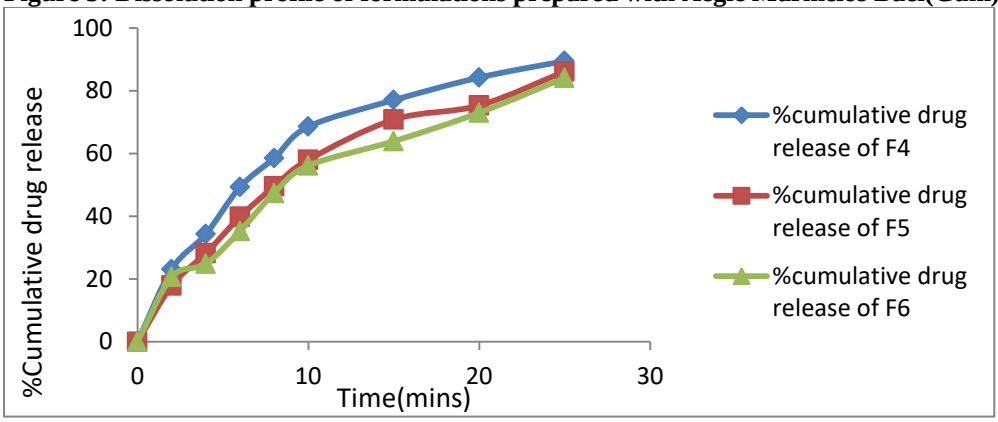
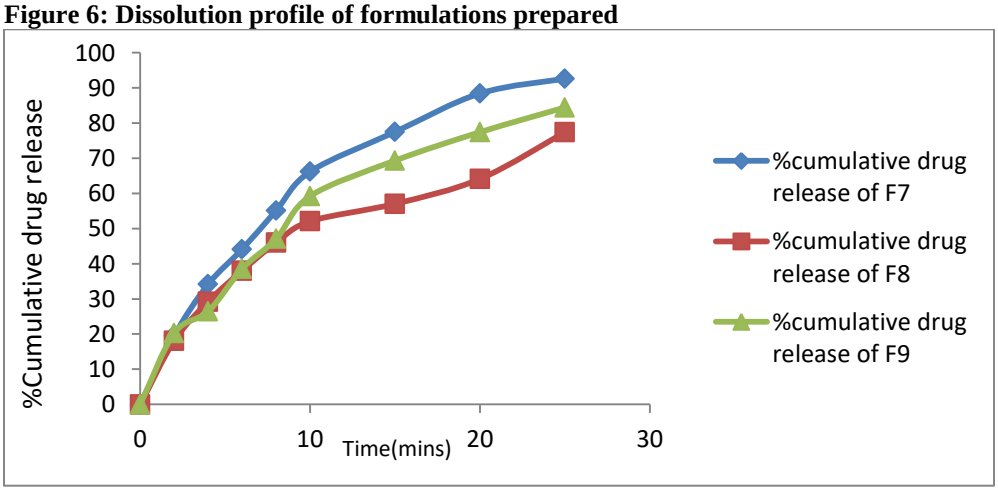


Figure 6: Dissolution profile of formulations prepared



With Locust bean gum as super disintegrate

From the tabular column 8.4 it was evident that the formulations prepared with super disintegrate Crospovidone showed maximum % drug release in 25 min i.e 97.62% (F1 formulations and the concentration of super disintegrate was 5 mg). So the principle of super disintegrates was found to be useful to produce Sublingual tablets. F1 formulation was considered as optimized formulation.

CONCLUSION

In the present work, an attempt has been made to develop Immediate release tablets of Metolazone. Crospovidone, Aegle Marmelos Bael(Gum) and Locust bean gum were employed as super disintegrating agents to

enhance the solubility and dissolution rate of selected drug molecule. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F1 formulation showed maximum % drug release i.e., 97.62 % in 25 min hence it is considered as optimized formulation. The F1 formulation contains crospovidone as super disintegrate in the concentration of 5 mg.

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