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Formulation and Evaluation of Fast Dissolving Tablet of Terazosin Hydrochloride

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ABSTRACT

Ethanol-induced memory impairment in rats is a consequence of changes within the central nervous system that are secondary to impaired oxidative stress and cholinergic dysfunction. Treatment with antioxidants and cholinergic agonists are reported to produce beneficial effects in animal models. Rutin is reported to exhibit antioxidant effect and cholinesterase (ChE) inhibitor activity. However, no report is available on the influence of rutin on ethanol-induced memory impairment. Therefore, we tested its influence against cognitive dysfunction in ethanol-induced rats using Morris water maze test and Novel object recognition test. Lipid peroxidation and glutathione levels as parameter of oxidative stress and ChE activity as a marker of cholinergic function were assessed in the cerebral cortex and hippocampus. Forty five days after ethanol treated rats showed a severe deficit in learning and memory associated with increased lipid peroxidation, decreased glutathione, and elevated ChE activity. In contrast, chronic treatment with rutin (20-80 mg/kg, p.o., once a day for 45 days) and vitamin C (100 mg/kg, p.o.) improved cognitive performance, and lowered oxidative stress and ChE activity in ethanol treated rats. In conclusion, the present study demonstrates that treatment with rutin prevents the changes in oxidative stress and ChE activity, and consequently memory impairment in ethanol treated rats.

Keywords: Rutin; Ethanol; Memory impairment; Oxidative stress; Morris water maze.

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INTRODUCTION

Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient, and most economical method of drug delivery. Oral route of drug administration become popular route for systemic effects due to ease of ingestion, accurate dosage, self-medication, pain avoidance. United States Food and Drug Administration (FDA) defined fast dissolving tablet (FDT) as "a solid dosage form containing medicinal substance or active ingredient which disintegrate or dissolve rapidly within seconds when placed upon the tongue."[1] The problem of gulping is a typical phenomenon in geriatric patients because of the dread of stifling, hand tremors, dysphasia and in schizophrenic patients which leads to poor patient compliance.[2]

To get the desired effect, the drug should be delivered to its site of action at such rate and concentration to achieve the maximum therapeutic effect and minimum adverse effect. For the development of a suitable dosage form a thorough study about the physicochemical principles that governs a specific formulation of a drug should be subjected[3].These are novel types of tablets that dissolve/ disintegrate/ disperse in saliva within few seconds without water. According to European pharmacopoeia, these MDTs should dissolve/disintegrate in less than three minutes[4].

Fast dissolving tablets dissolve or disintegrate in the oral cavity without the need of water. Most fast-dissolving tablets must include substances to mask the bitter taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients[5]. Presently, increasing attention has been paid for orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in the mouth[6].

Fast Dissolving Tablets

A fast dissolving tablet is a solid dosage form that can disintegrates into smaller granules which slowly dissolve in the mouth. The disintegration time for fast dissolving tablet varies from a few seconds to more than a minute depending on the formulation and the size of the tablet.

A fast disintegrating or dissolving system or tablet can be defined as a solid dosage form that can disintegrate or dissolve within 30 seconds, in the oral cavity resulting in a solution or suspension without administration of water. The fast disintegrating tablets are synonymous with fast dissolving tablets; melt in mouth tablets, rapimelts, Porous tablets, Orodispersible, quick dissolving or rapidly disintegrating tablets.

Need for the development of FDT'S

Fast dissolving dosage forms are suitable for those patients (particularly pediatric and geriatric patients) who are not able to swallow traditional tablets and capsules with an 8-oz glass of water.

These include the following:

- Patients who have difficulty in swallowing or chewing solid dosage forms.
- Patient's incompliance due to fear of choking.
- Very elderly patients with depression may not be able to swallow the solid dosage forms.
- An eight-year-old patient with allergies desires a more convenient dosage form than antihistamine syrup.
- A middle-aged patient undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2- blocker.
- A schizophrenic patient who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic.

The objective of present research work was to develop fast dissolving tablet of Terazosin Hydrochloride. The oral Route of administration is considered as the most widely accepted route, but the drawback of the commonly used oral dosages forms like tablets and capsules is difficulty in swallowing leading patients incompliance, particularly in case of pediatric and geriatric patient. Thus, a new delivery system i.e. fast dissolving tablet is developed. Fast dissolving tablet constitutes an innovative dosage form that overcome the problem of swallowing and provides a quick onset of action.

The major claim of fast dissolving tablet is to increase its bioavailability as well as patient compliance compound to traditional tablets. Because of adsorption through oral cavity there can be pre-gastric adsorption occurs which avoids the fast pass metabolism of drug formulation. Fast dissolving tablet is dissolve in oral cavity and drug absorbs through oral cavity which provides rapid effect and requires less time to achieve maximum plasma concentration.

According to classification Terazosin HCl is in a class of medications called alpha- blockers. Terazosin Hydrochloride is a white powder, relatively soluble in water. Solubility and dissolution was improved by formulating solid dispersion. Keeping in view the advantages of this delivery system, in the present study, attempts were made to formulate immediate dissolving tablet Terazosin Hydrochloride. Which is useful to reduce blood pressure level in the treatment of antihypertensive agents. The direct compression was used to compress the tablets as it is the easiest way to manufacture tablets. Conventional equipments, commonly available excipients and limited number of processing steps are involved in direct compression and so manufacturing cost is low.

MATERIALS AND METHOD

Terazocin Hydrochloride was obtained as a gift sample from Modern lab (Indore M.P. India) &

Crosspovidone, Sodium starch glycolate, Crosscamellose sodium, Microcrystaline cellulose, Mannitol, Sodium saccharine, Talc, Magnesium strearete are provide by the institute and other reagent used are of analytical grade .

Preformulation Study:

The preformulation study is one of the important prerequisites for the development of any drug delivery system. It provides the information necessary to define the nature of the pharmaceutical substance and provides a structure for the combination of drugs with pharmaceutical excipients in the dosage forms. Therefore, preformulation studies were performed on the drug sample obtained for identification, including solubility analysis, melting point determination and compatibility studies.

Physical Appearance: (Organoleptic Character):

Terazocin HCl was physically characterized by its appearance, color and odor. All these physical parameters were recorded and compared with the value of the literature. Sometimes organoleptic tests are performed to determine that pharmaceutical products can transfer flavors or odors to the materials and components in which they are packaged. Life studies often use taste, sight and smell to determine if a product is safe to consume.

Determination of melting point:

The determination of the melting point of the obtained sample was carried out because it is a good first indication of the purity of the sample, since the presence of a relatively small amount of impurities can be detected by a reduction and widening in the melting point range. The melting point of Terazocin HCl was determined by the capillary fusion method; Capillary closed on one side full of drugs and placed in the melting point apparatus. The temperature at which the solid drug becomes liquid has been observed and compared with the value of the literature.

Solubility Profile of Terazosin HCl:

Solubility can be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A solubility analysis of the preformulation was performed, which includes the selection of the suitable solvent system to dissolve the respective drug. The solubility of Terazosin HCl has been determined in different solvents. An excess amount of the drug in 10 ml of each solvent was added in glass tubes with screw caps and stirred for 12 hours at room temperature. The solution was filtered, diluted and the solubility determined.

Calibration Curve of Drug:

Measurement of spectra of Terazosin Hydrochloride using UV visible 1600 Shimadzu double beam spectrophotometer and the solvent used for dilutions was 0.1 N NaOH for Terazosin

Hydrochloride. The standard solution of Terazosin Hydrochloride was scanned in range of 200 to 400nm and λ_{max} was determined.

Pre-compression studies of formulated fast dissolution tablets of Terazosin Hydrochloride:

The evaluations of Pre-compression studies of formulated fast dissolution tablets of Terazosin Hydrochloride were done as per standard procedures. The following parameters were evaluation.

Bulk density:

Bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V) and weight of the powder (M) was determined. The bulk density was calculated by using the below mentioned formula,

Bulk density = Mass of granules / Volume of granule

Angle of Repose –

The angle of repose was determined by the funnel method suggested by Newman. Approximately 5gm of powder was poured through a glass funnel from a height of 6 centimeter onto a level bench top. The angle that the side of the conical heap made with the horizontal plane was recorded as the angle of repose. Angle of repose is determined by the following formula,

Tan θ = h/r

Determination Tapped Density –

20 g of the mixed blend (W) was introduced into a 100 ml measuring cylinder, and the Initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The tapped density were calculated using the following formulae.

Tapped density = W / VF

Carr's Index:

Carr's index (Compressibility Index) is a measure of the tendency of the powder to be compressed. It was determined by bulk and tapped densities and was calculated using the following formula:

Carr's Index = ρt - ρb/ρt ×100

Hausner's Ratio:

It is the ratio of tapped density to the bulk density.

Hausner's Ratio = Tapped density / Bulk density

Drug –Excipient Interaction Study:

The compatibility of drug and various excipients was studied by thin Layer Chromatography (TLC) technique. For study purpose, Terazosin Hydrochloride 10mg mixed thoroughly by mortar and pestle with excipient in ratio of 1:5respectively and placed in tightly closed vials. All vials

were kept at 40 ºC for 4 weeks.

Mobile phase preparation for Terazosin Hydrochloride is Chloroform: Toluene: Methanol in the ratio 9:1:6

Formulation of fast dissolution tablet:

Terazosin Hydrochloride fast dissolution tablets were prepared by the direct compression method using different excipients. The excipients used were Micro crystalline cellulose (binding agent), mannitol (diluents), sodium saccharine (sweetening agent), Crospovidone, Sodium starch glycolate and Croscarmellose sodium (super disintegrants). Different concentrations of excipients were used to prepare different formulations of sublingual tablets. All the ingredients of the sublingual tablets of Terazosin Hydrochloride were weighed and mixed in mortar with the help of pestle. Then the blended material was slightly compressed on the 6mm flat–biconvex punch using a Rimek MINI PRESS-I MT tablet machine.

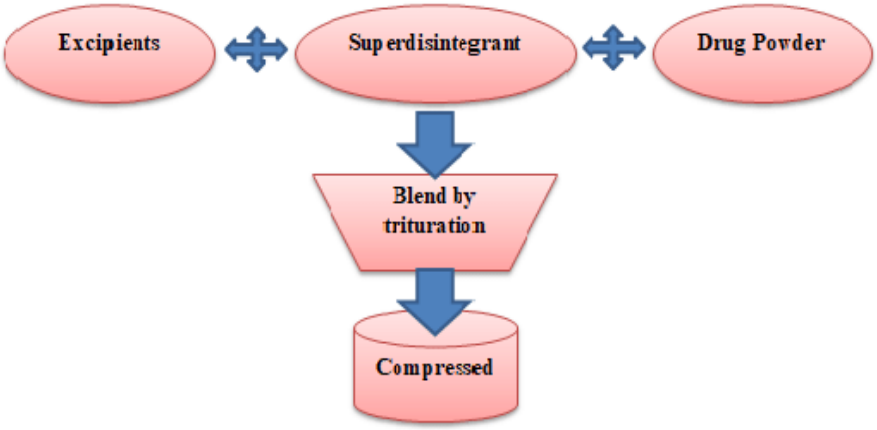


Figure 1: Formulation of table

Table1: Drug–Excipient Interaction

S. No.	Ingredients	F1	F2	F3	F4	F4	F6
1	Drug	10	10	10	10	10	10
2	Crosspovidone	2	4	-	-	-	-
3	Sodium starch glycolate	-	-	2	4	-	-
4	Crosscamellose sodium	-	-	-	-	2	4
5	Microcrystalline cellulose	45	40	45	40	45	40
6	Mannitol	53	56	53	56	53	56
7	Sodium saccharine	10	10	10	10	10	10
8	Talc	2	2	2	2	2	2
9	Magnesium strearete	3	3	3	3	3	3
	Total wt. in mg	**125**	**125**	**125**	**125**	**125**	**125**

Post-compression studies formulated fast dissolving tablets of Terazosin Hydrochloride:

The evaluations of Post-compression studies of formulated sublingual tablets of Terazosin

Hydrochloride were done as per standard procedures The following parameters were evaluation.

Shape and Color of Tablets:

Randomly picked tablets from each formulation batch examined under lens for shape and in presence of light for color. The tablet shows round shape, white in color. All ingredients used were white in color. There was no change in color and odor of the tablets in all the formulations. It indicates that all the excipients used were compatible with the drug and did not cause any chemical reaction that affects the properties of formulation

Weight variation:

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Specification of Weight variation as per I. P.

Hardness:

Hardness or tablet crushing strength, the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm2.

Friability:

The friability of tablets using 10 tablets as a sample was measured using a Roche Friabilator. Tablets were rotated at 25 rpm for 4 minutes or up to 100 revolutions. The tablets were taken out, dedusted and reweighted. The percentage friability was calculated from the loss in weight as given in equation below. The weight loss should not more than 1%.

%Friability = (Initial weight – Final weight) x 100 (Initial weight)s

Water Absorption Ratio:

A piece of tissue paper folded twice was kept in a Petri dish (internal diameter 5.5 cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and reweighted. Water absorption ratio, R was determined according to the following equation.

$$R = (W_a - W_b)\ 100 / W_b$$

Tablet thickness:

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

Uniformity of thickness:

Thickness can be measured using a simple procedure. A total of 5 tablets were taken and their thicknesses measured using Vernier calipers. The thickness was measured by placing the tablet between the two arms of the Vernier calipers.

Drug content analysis:

Total 110 tablets were weighed and powdered. The powder equivalent to Terazosin Hydrochloride was taken and dissolved in 0.1N Hydrochloride. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically at 314 nm

Wetting time:

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. According to the following equation proposed by Washburn E.W (1921), the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders.

$$dl/dt = r\gamma cosq/(4ql)$$

In-vitro disintegration time:

Disintegration time is an important characteristic of orally disintegrating tablets (ODTs), and evaluation of disintegration time is a key step in formulation development, manufacturing, and clinical practice.

RESULTS AND DISCUSSION

Pre-formulation studies

Table 2: Properties of Terazosin HCl

S. No.	Parameters	Observation
1	Colour	White
2	Odour	Odourless
3	Taste	Better

Solubility Properties:

The solubility of Terazosin Hydrochloride is various Aqueous and Non Aqueous Solvents was checked and in Water is found to be 0.132 mg/ml.

Table 3: Solubility Profile of Terazosin Hydrochloride

S. No.	Solvent	Terazosin Hydrochloride
1	0.1N HCl	Soluble
2	Water	Soluble
3	Methanol	Soluble
4	Ethanol	Soluble
5	Chloroform	Insoluble

Melting point:

The melting point of Terazosin Hydrochloride was found to be 271- 274 ^{0}C $\pm$5 and the drugs was found to be in the pure form.

Table 4: Melting point of Terazosin Hydrochloride

Drug	Range	Melting point
Terazosin Hydrochloride	271- 274 ^{0}C	272° C

Calibration curve:

The λ_{max} for Terazosin Hydrochloride was found to be 254nm. Calibration curve was prepared, for the drug. Linear relationship was observed in the conc. Of 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml. Correlation coefficient was found which was within the limit.

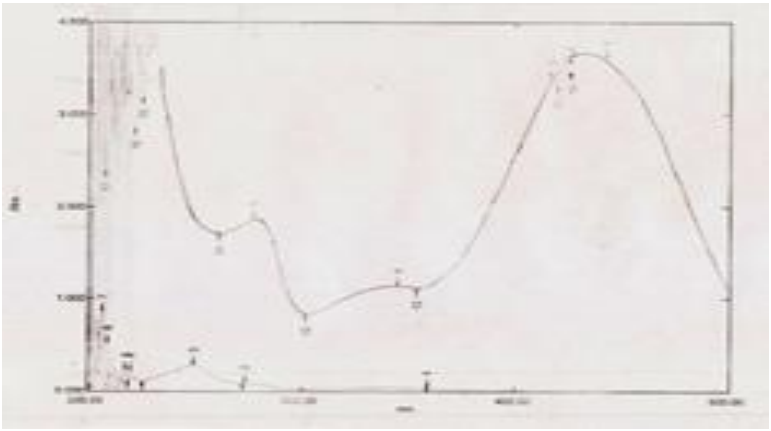
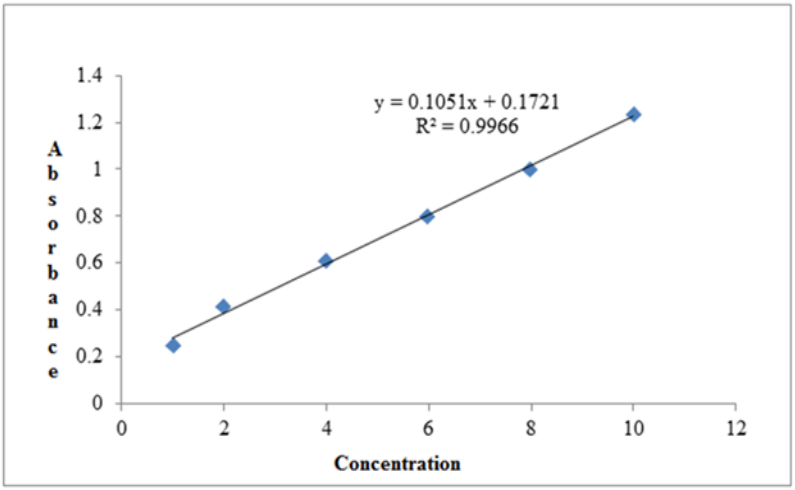


Figure 2: UV Spectra of Terazosin Hydrochloride

Table 5: Calibration curve for Terazosin Hydrochloride

S.NO.	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.237
3	4	0.382
4	6	0.578
5	8	0.682
6	10	0.852



Drug excipients interaction study

Tablet 6: Interaction Study of Terazosin HCl

S. No.	Parameter	Initial	After 4 week	Observation
1	Pure Drug	White	No change	No change
2	Drug + Cross Carmellose Sodium	White	No change	No change
3	Drug + Sodium starch glycolate	White	No change	No change
4	Drug + Cross povidone	White	No change	No change
5	Drug + Microcrystalline cellulose	White	No change	No change
6	Drug + Mannitol	White	No change	No change
7	Drug + Sodium saccharine	White	No change	No change
8	Drug + Talc	White	No change	No change
9	Drug + Magnesium stearate	White	No change	No change

Evaluation of fast dissolving tablets of Terazosin Hydrochloride

Pre-compression parameters:

Properties of drug were determined. All the results were under the limit

Table 7: Pre – compression parameters

Drug	Bulk density Pb = M/Vb	Tapped density pt =M/Vt	Angle of repose Tan $\theta = h/r$	Compressibility Index Pt –pb/pt ×100	Hausner's ratio pt/pb
Terazosin Hydrochloride	0.52 ± 0.56	0.62 ± 0.65	18.98 ± 24.34	13.84 ± 16.12	1.16 ±1.19

All values are expressed as mean ± standard deviation, n=3

Post compression parameters:

Evaluation of post compression parameter was performed. Hardness was found to be in range of 2.7 to 3.3 kg/cm^2 for all the formulation indicating good mechanical strength. Thickness of all formulations was found in the range of 2mm to 2.2mm in all he formulations the friability values are less than 1% and meet the IP limit.

Table 8: Post Compression Parameter-I

Formulation	Thickness (mm±SD) (n = 5)	Hardness (Kg/cm^2± SD) (n=5)	Weight variation (avg. Wt.±%SD) (n=20)	Friability (%)
F1	2.2±0.20	2.3±0.27	260±0.52	0.68
F2	2.2±0.16	2.6±0.41	242±0.35	0.70
F3	2.1±0.16	2.0±0.27	244±0.72	0.71
F4	2.3±0.14	3.0±0.49	248±0.37	0.70
F5	1.9±0.30	3.2±0.27	240±0.48	0.73
F6	1.8±0.32	3.3±0.41	239±0.32	0.78

All values are expressed as mean ± standard deviation, n=3

All formulations passed weight variation test as the percentage weight variation was within the pharmacopoeia limits. Water absorption ratio of all formulation was found between 32.10 to 39.01%. Wetting time was found to be between 26-42 sec ranges. Disintegration time was found

between the range of 20 to 32 sec. Cross caramelise sodium was used as super disintegration agent, the tablet disintegration rapidly within less time due to easy swelling ability of Cross Carmellose sodium.

Table 9: Post Compression Parameter-II

Formulation	Disintegration time (sec) (Avg±Sd)	Wetting time (sec) (Avg±SD)	Water absorption ratio (%) (Avg±SD)
F1	22±1.00	28±0.57	72±2.05
F2	20±1.52	26±0.57	81±1.52
F3	28±0.57	31±1.52	60±0.37
F4	32±1.15	32. ±1.00	62±2.08
F5	29±0.57	39±1.00	51±1.01
F6	30±1.00	42±0.51	55±0.57

All values are expressed as mean ± standard deviation, n=3

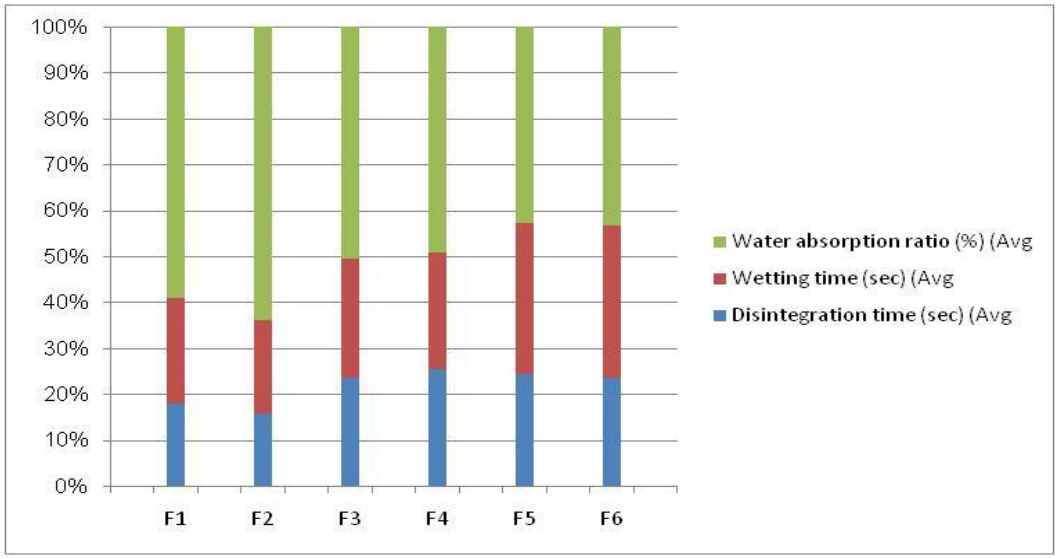


Figure 5: Water absorption, Wetting time, Disintegration time of all formulation

CONCLUSION:

Physical observation and TLC studies were used to determine API nature and excipient compatibility. API and all selected excipients exhibited no interaction. Direct compression method was used to successfully manufacture. The tablets were examined pre- and post-compression as per standards. Results met pharmacopoeia standards. By evaluating all the parameter of all six formulation F2 formulation was found to be the best formulation. The disintegration time, wetting time, water absorption Ratio of F2 formulation was found to be 20±sec, 26±0.57 sec, 81±1.52% respectively & drug content was found to be 98.69% for Terazosin Hydrochloride. Hence it was concluded that F2 formulation contacting croscarmellose sodium as the superdisintegrants was ideal. Effectiveness of disintegrants can be ordered as follows: croscarmellose sodium > microcrystalline >cellulose> sodium starch Glycolate.

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