FORMULATION AND EVALUATION OF FAST DISSOLUTION TABLET OF DOXAZOSIN MESYLATE

Rewati Raman [1], Sandeep sahu [2], Ritesh Jain [3], Suruchi Prasad [4], Satish sahu [5],

School Of Pharmacy Chouksey Engineering Collage Bilaspur Chhattisgarh India.

Abstract: Tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing. Patients often experience difficulty in swallowing conventional tablets when water is not available nearby. *According to European pharmacopeia, these MDTs should dissolve in less than three minutes.* The formulation is more useful for the bed ridden and patients who have the swallowing problem. Solid dispersion is one of the accepted approaches for dissolution enhancement. They are molecular mixtures of poor water-soluble drugs with hydrophilic carriers prepared by solvent evaporation and melting method. Doxazosin mesylate (DM), a quinazoline derivative, could be used in the treatment of mild to moderate hypertension and also in the management of symptomatic benign prostatic hyperplasia (BPH). In hypertensive patients, DM reduces the blood pressure by selective antagonizing the postsynaptic alpha1 adrenergic receptors

Keyword: mouth dissolving tablet, solid dispersion, doxazosin.

Tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing. Patients often experience difficulty in swallowing conventional tablets when water is not available nearby. *According to European pharmacopeia, these MDTs should dissolve in less than three minutes.* The formulation is more useful for the bed ridden and patients who have the swallowing problem. The benefits of MDTs is to improve patients compliance, rapid onset of action, increased bioavailability and good stability which make these tablets popular as a dosage form of choice in the current market.

1.1 *Fast Dissolving Tablets*

1.1.1 *Definition:*

United states food and drug administration (FDA) defined fast dissolving tablets (FDT) as a solid dosage form containing medical substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue prepared by direct compression method. The disintegration time for FDTs generally ranges from several seconds to about a minute.

1.1.2 *Advantages of FDTS*

- Ease of administration to geriatric, pediatric mentally disabled and bed-ridden patients who have difficulty in swallowing the tablet.
- Bioavailability of drugs is enhanced due to absorption from pharynx and esophagus.
- Rapid onset of therapeutic action as tablets is disintegrated rapidly along with quick dissolution and absorption in oral cavity.
- Rapid drug therapy intervention is possible.
- No specific packaging is required. it can be packaged in push through blisters.

1.1.3 Disadvantages of FDTS

- It is hygroscopic in nature so it must be kept in dry places.
- High dose cannot be incorporated into tablet.
- Eating and drinking may become restricted.
- Buccal tablet is moisture sensitive.
- 1.1The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave unpleasant taste and grittiness in mouth if not formulated properly.

1.1.4 *Method of preparation of FDTS*

- Freeze drying/lyophilization
- Tablet melding
- Spray drying
- Sublimation
- Direct compression
- Mass extrusion

1.1.4.1 ***Freeze drying/lyophilization:*** A process, in which water is sublimated from the product after freezing, is called freeze drying. Freeze-dried forms offer more rapid dissolution than other available solid products. The lyophilisation process imparts

glossy amorphous structure to the bulking agent and sometimes to the drug, thereby enhancing the dissolution characteristics of the formulation

1.1.4.2 *Tablet moulding*

In this method, moulded tablets are prepared by using water-soluble ingredients so that the tablets dissolve completely and rapidly.

1.1.4.3 *Spray drying*

This technology produces highly porous and fine powders as the processing solvent is evaporated during the process. This formulation technique gives porous powder and disintegration time < 20 sec.

1.1.4.4 *Sublimation*

The presence of a highly porous structure in the tablet matrix is the key factor for rapid disintegration of MDTs. Even though the conventional tablets contain highly water-soluble ingredients, they often fail to disintegrate rapidly because of low porosity. Camphor was sublimated in vacuum at 80°C for 30 min after preparation of tablets.

1.1.4.5 *Direct compression method*

This technique is easy way to formulate MDTs since limited number of processing steps, low manufacturing cost and also accommodate high dose the final weight of tablet can easily exceed that of other production method.

1.1.4.6 *Mass extrusion*

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets.

1.2 *Doxazosin Tablets*

Molecular weight: 547.6g/mol

Formula: C22H29N5O8S

IUPAC name: [4-(4-amino-6, 7-dimethoxyquinazolin-2-yl) piperazin-1-yl] - (2, 3-dihydro-1, 4benzodioxin-3-yl] methadone.

Trade name: Cadura, Carduran, Cardular.

Solubility: slightly soluble in water.

Appearance: White crystalline powder

Bioavibility: 65%

Structure:

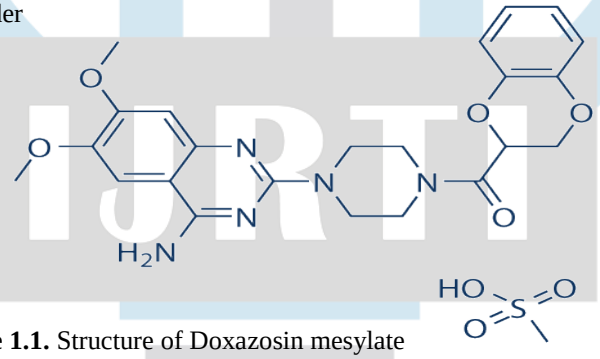

Figure 1.1. Structure of Doxazosin mesylate

1.2.1 *Definition*

Doxazosin oral tablet is a prescription drug. It comes in immediate-release and extended-release forms. Doxazosin oral tablets are available as the brand-name drugs **Cardura (immediate release).** The immediate release of Doxazosin is used to treat benign prostatic hyperplasia (BPH). The immediate release tablets are also to treat high blood pressure.

1.2.2. Preparation of Doxazosin tablet:

Doxazosin mesylate tablets each containing 4mg of Doxazosin mesylate were prepared by direct compression method according to formula. The different superdisintegrants used were sodium starch glycollate, croscarmellose sodium and crosspovidone in different concentrations. Blend was prepared by first passing all the ingredients through 60-mesh sieve separately and collected. The drug and microcrystalline cellulose were mixed in small portion of both at each time and blended to get a uniform mixture and kept aside. Then the other ingredients were weighed and mixed in geometrical order and the tablets were compressed using flat face 6.3 mm size punch to get a tablets of 100 mg weight using ten station cemach compression machine.

1.2.3 *Mechanism of action of Doxazosin*

The mechanism of action of Doxazosin mesylate (CARDURA) is selective blockade of the alpha 1 (postjunctional) subtype of adrenergic receptors. Studies in normal human subjects have shown that Doxazosin competitively antagonized the pressor

effects of phenylephrine (an alpha 1 agonist) and the systolic pressor effect of norepinephrine. The antihypertensive effect of CARDURA results from a decrease in systemic vascular resistance. The parent compound Doxazosin is primarily responsible for the antihypertensive activity.

Table 1.1. Excipients used in fast dissolving tablets

S.No	Name of excipients	Application
1	Super disintegrates	Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranular.
2	Bulking materials	Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth.
3	Lubricants	Lubricants remove grittiness and assist in the drug transport mechanism from the mouth doun into the stomach.
4	Taste masking	Flavoring and perfuming agents can be obtained from either natural or synthetic sources.
5	Emulsifying agent	Emulsifying agent in useful in stabilizing the immiscible blends and enhancing bioavailability.

2.0 Result and discussion:

2.1. Standard curve of doxazosin mesylate: Preparation of Standard Stock Solution and Calibration Curve Standard stock solution was prepared by dissolving Doxazosin Mesylate in 0.01 N HCl to make final concentration of 100 µg/ml. Different aliquots were taken from stock solution and diluted with 0.01 N HCl separately to prepare series of concentration from 2 – 10 µg/ml. An independent stock solution of 5 µg/ml was also prepared. The λ max was found by UV spectrum of Doxazosin Mesylate in 0.01 N HCl, in range of 200 – 400 nm and it was found to be 245 nm as shown in Fig 1. Absorbance was

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	2	0.112
3	4	0.191
4	6	0.287
5	8	0.378
6	10	0.452

Measured at 246 nm against 0.01 N HCl as blank. The calibration curve was prepared by plotting absorbance versus concentration of Doxazosin Mesylate.

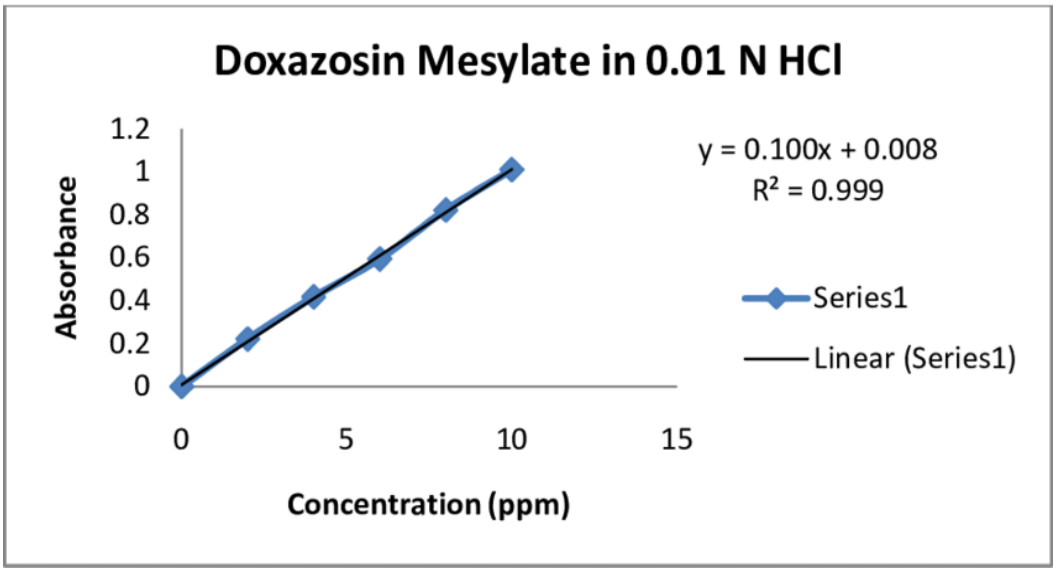

Table 2.2. Physiochemical evaluation of doxazosin mesylate:

Formulation	Angle of repose (°)	Bulk density (g/cm^3)	Tapped density (g/cm^3)
F1	30.21	0.365	0.572
F2	30.42	0.318	0.582
F3	30.84	0.393	0.512
F4	30.53	0.322	0.535
F5	30.85	0.341	0.513
F6	30.26	0.394	0.555
F7	30.94	0.344	0.536
F8	30.74	0.392	0.587

Table 2.3. Compressibility index and Hausner ratio

Formulation	Compressibility index(%)	Hausner's ratio
F1	23.1	1.23
F2	21.5	1.53
F3	19.3	1.33
F4	19.4	1.32
F5	20.3	1.23
F6	18.7	1.41
F7	20.3	1.43
F8	19.9	1.25

Table 2.4. Hardness and friability

Formulation	Hardness (kg/cm^3)	Weight Variation (mg)	Friability (%)
F1	2.9	147.3±4.6	0.56
F2	3.0	146.9±5.2	0.78
F3	3.1	148.4±4.4	0.57

F4	3.1	147.1±4.9	0.61
F5	3.2	147.7±4.7	0.70
F6	3.0	144.9±6.2	0.63
F7	2.8	148.7±4.6	0.55
F8	2.9	148.1±3.9	0.61

Table 2.5. Thickness and diameter

Formulation	Thickness (mm)	Diameter (mm)
F1	2.6	6.8
F2	2.6	6.8
F3	2.6	6.8
F4	2.6	6.8
F5	2.6	6.8
F6	2.6	6.8
F7	2.6	6.8
F8	2.6	6.8

Table 2.6 disintegration of doxazosin mesylate tablet:

Formulation	Drug content (%)	Disintegration Time (sec)
F1	98.12	183
F2	97.23	97
F3	99.01	87
F4	98.23	65
F5	99.21	54
F6	97.13	76
F7	98.65	64
F8	97.78	54

Table 2.7 Drug release profile:

Formulation	% drug release in 2min.	% drug release in 4min.	% drug release in 6min.	% drug release in 8 min.	% drug release in 10 min.	% drug release in 15 min.	% drug release in 20min	% drug release in 25 min.
F1	34.5	42.6	54.02	61.8	65.9	72.0	74.3	79.8

F2	36.0	43.0	51.3	59.6	68.2	75.3	80.0	87.4
F3	35.2	41.9	53.8	62.1	72.0	80.0	89.0	98.3
F4	37.3	43.0	55.0	63.8	75.0	81.1	90.8	98.7
F5	36.8	39.8	53.7	60.0	69.3	78.6	88.9	98.3
F6	30.5	37.9	48.3	59.7	66.8	76.0	81.8	87.9
F7	32.8	41.3	51.8	62.0	68.6	79.6	85.0	93.9
F8	38.0	43.0	50.8	61.9	69.1	80.0	89.0	96.5

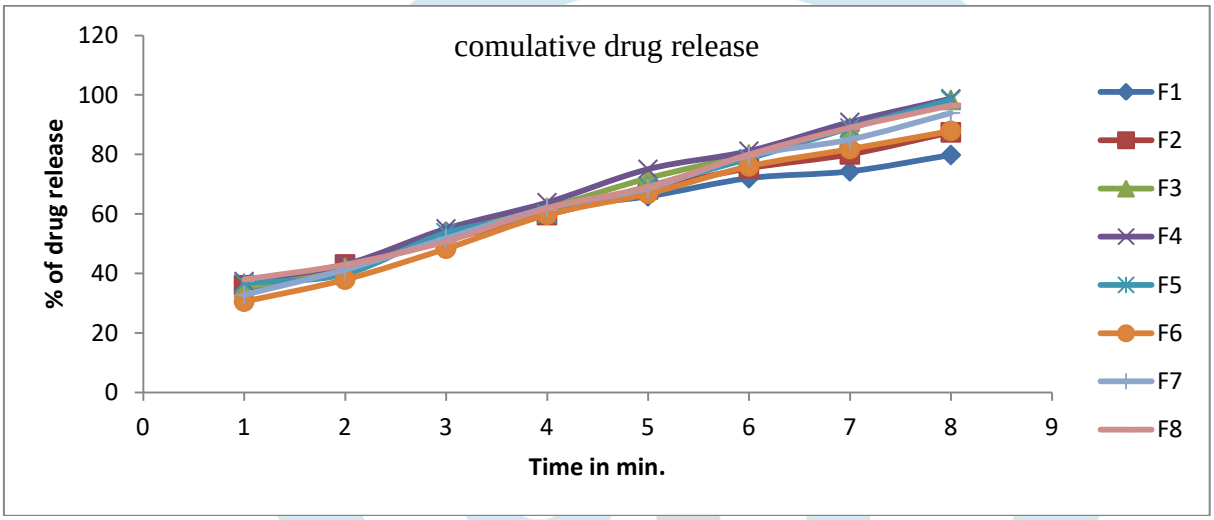

Fig 2. Drug release data profile

2.8. Stability study: The sample was subjected for stability studies under room temperature. The solution was stable for up to 5 hours with % R.S.D. less than 1 as shown in table no.2.8

Table 2.8 for Stability study:

Storage period	% conc. Of Drug	Stored at 25ºC/60% RH % CDR	Stored at 40ºC/75% RH % CDR
Initial	99.6	98.6±0.5	98.7±0.5
After 1 week	99.4	98.5±0.5	98.5±0.5
After 2 week	99.1	98.1±0.5	97.8±0.5
After 3 week	98.8	97.6±0.5	97.7±0.5
After 4 week	98.6	97.3±0.5	97.4±0.5

Conclusion:

From the present research work that is “Formulation and evaluation of Doxazosin mesylate fast dissolving tablet” for anti-hypertensive the following point were concluded

- In the beginning blank polymeric tablet were prepared by solvent casting technique using HPMC E15, PVP K-30, PVA, the concentration of polymer was varied and the best formulations were chosen for incorporating the drug.
- The prepared tablet were evaluated for following parameters like physical appearance and surface texture, weight uniformity, thickness, and drug content uniformity, disintegration, permeation study, drug excipients interaction studies, in vitro drug release and short-term stability studies.
- All the formulation showed acceptable quality control property formulation F4 having polymer concentration HPMC and PVP K30 (3:2) gave better drug release rate over period of 8 minutes thus formulation F4 was found to be the most promising formulation on the basis of acceptable evaluation property and the Invitro drug release rate of 98.7 %. Based on the FTIR studies appear to be no possibility of interaction between the Doxazosin mesylate and polymers of other excipients used in the tablet.
- Stability studies were conducted for the optimized formulation as per ICH guidelines for a period of 30 days which revealed that the formulation was stable. The result suggests that the developed fast release strips of Doxazosin mesylate could perform the better than conventional dosage form leading to improved efficacy and better patient compliance.

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Reference:

1. Doxazosin Mesylate, British Pharmacopoeia 2010, Vol I, 750-752.
2. R. Sundaraganapathy, M. Jambulingam, U. Subasini, Int. J. Pharm. Ind. Research., 2011, 1 (1):28-31
3. Fatema K., Rahman Z., Biswas S.K., Akhter, S. J. Pharm. Sci., 2010,3(1): 4-10.
4. R.S. Nijhu, D.T. Akhter, Int. Curr. Pharm.J. 2011, 1 (1):1-5.
5. I.Savic, G.Nikolic, V.Bankovic, Macedonian J.Chem.Chem.Engg. 2008, 27 (2):149-156.
6. B.Dhanya, A. Suganthi, A. K. Seth, Indian J.Pharm.Sci. 2011, 73 (1):120-122.
7. C.Sitaram, B.N.Reddy, C.S.P. Sastry, Indian J.Pharm.Sci.2011, 73 (1):107-110.
8. ICH Guideline Q2 (R1), Validation of Analytical Procedures: Text and Methodology.
9. Parmar A.R., Bhakhar D.N., Shah K.N. and Vekariya K.V., Der Pharmacia Sinica, 2012, 3(3)
10. Shojaei AH, 1998. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharm Sci, 1998; 1: 15-30.
11. Gupta Sachin, Srivastav Shruti, Vajpai Meenakshi Journal of Pharmacy Research, 2010; 3(4).
12. Betageri GV, Makarla KR. Int J Pharm, 1995; 126(1): 155-160.
13. Morris KR, Knipp GT and Serajuddin ATM J. Pharm. Sci., 1992; 81: 1185-1188.
14. Narang N, Sharma J. Sublingual mucosa as a route for systemic drug delivery.Int J Pharm Pharmaceut Sci, 2011; 3(2): 18-22.
15. Browhn GL. Formation of films from polymer dispersions. J Polym Sci., 1956; 22(102): 423-434.