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FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLET OF DOXAZOSIN MESYLATE FOR THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT

The objective of the present study was to develop sustained release tablets of Doxazosin Mesylate. The tablets were prepared by direct compression method the polyemer are used in the formulation are HPMC K-100, Xanthan gum and Ethyl cellulose with different ratios. The powder were evaluated for angle of repose, bulk density, compressibility index and drug content. The tablets were subjected to weight variation test, drug content, hardness, friability and *in vitro* drug release studies. The tablets showed satisfactory flow properties, compressibility and drug content. All the tablets formulation showed acceptable pharmacotechnical properties. The results of dissolution studies indicated that formulation DM4 drug and xanthan gum could sustained the drug release up to 12hrs.The most successful formulation of the study exhibited satisfactory drug release.

KEYWORDS: Doxazosin Mesylate, sustained Release, Direct Compression Method.

INTRODUCTION

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body.[1] This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action.[2, 3] The term therapeutic substance also applies to an agent such as gene therapy that will induce in vivo production of the active therapeutic agent. Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect.[4] The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.[5, 6]

The first sustained release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida.

Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ.[7,8]

Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulations.

- ✓ If the active compound has a long half-life, it is sustained on its own,
- ✓ If the pharmacological activity of the active is not directly related to its blood levels,
- ✓ If the absorption of the drug involves an active transport and

- ✓ If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.

The above factors need serious review prior to design. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed.[9]

In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

1.1. Rationale for extended release dosage forms

Some drugs are inherently long lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up doses, and noncompliance with the regimen.[10,11] When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose. However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of sub therapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient. Extended-release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended-release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period (Fig.1).

The sustained plasma drug levels provided by extended-release products oftentimes eliminate the need for night dosing, which benefits not only the patient but the caregiver as well.[12]

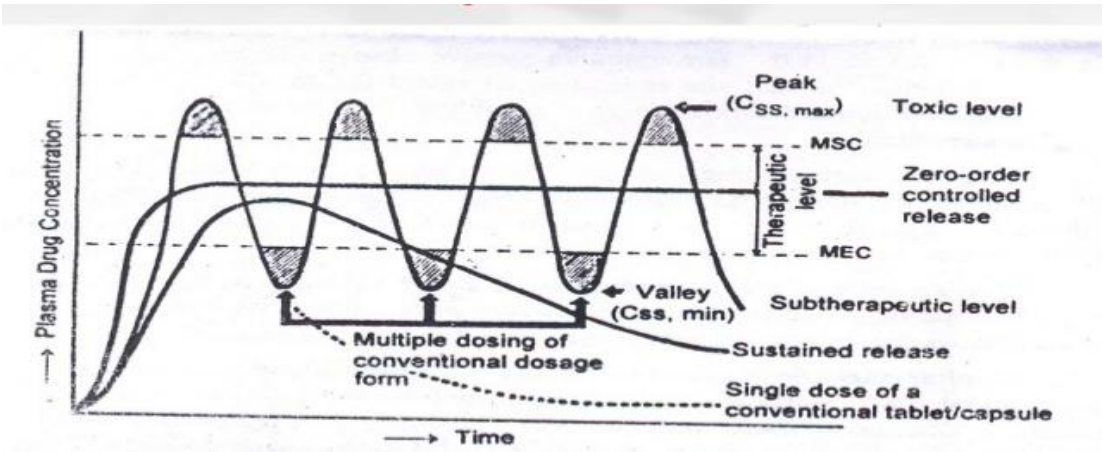

Figure 1.1: Hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations.

1.2. Advantages of sustained release dosage forms

- The frequency of drug administration is reduced.
- Patient compliance can be improved.
- Drug administration can be made more convenient as well.

- The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.
- Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced.
- The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.
- The total amount of drug administered can be reduced, thus.
  - Maximizing availability with minimum dose;
  - Minimize or eliminate local side effects;
  - Minimize or eliminate systemic side effects;
  - Minimize drug accumulation with chronic dosing.
- Safety margins of high potency drugs can be increased a the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.
- Improve efficiency in treatment.
  - Cure or control condition more promptly
  - Improve control of condition
  - Improve bioavailability of some drugs
  - Make use of special effects; e.g. sustain release aspirin for morning relief of arthritis by dosing before bed-time.

Disadvantages of sustained release dosage forms

- Probability of dose dumping.
- Reduced potential for dose adjustment.
- Cost of single unit higher than conventional dosage forms.
- Increase potential for first pass metabolism.
- Requirement for additional patient education for proper medication.
- Decreased systemic availability in comparison to immediate release conventional dosage forms.
- Poor in*vitro* and in*vivo* correlations.

Terminology

Modified release delivery systems may be divided conveniently in to four categories.

A) Delayed release

B) Sustained release

✓ Controlled release

✓ Extended release

C) Site specific targeting

D) Receptor targeting

A) Delayed Release

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.[14]

B) Sustained release

During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the technology of sustained release is also being applied to veterinary products. These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.[15]

1. Controlled Release

These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

2. Extended Release

Pharmaceutical dosage forms release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds.

C) Site specific targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

D) Receptor targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be sustained drug delivery systems.

1.4. Design and formulation of oral sustained release drug delivery system

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form would encounter during its transit, the gastrointestinal motility, the enzyme system and its influence on the drug and the dosage form. The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood level time profile similar to that after intravenous constant rate infusion.

Sustained (zero-order) drug release has been attempted to be achieved with various classes of sustained drug delivery system.[14,16,17]

A) Diffusion sustained system.

i) Reservoir type.

ii) Matrix type
B) Dissolution sustained system.
i) Reservoir type.
ii) Matrix type
C) Methods using Ion-exchange.
D) Methods using osmotic pressure.
E) pH independent formulations.
F) Altered density formulations.

MATERIALS

Doxazosin mesylate-Provided by SURA LABS, Dilsukhnagar, Hyderabad, HPMC K-100-Merck Specialities Pvt Ltd, Mumbai, India, Xanthan gum-Merck Specialities Pvt Ltd, Mumbai, India, Ethyl cellulose- Merck Specialities Pvt Ltd, Mumbai, India, PVP-Merck Specialities Pvt Ltd, Mumbai, India, Lactose-Merck Specialities Pvt Ltd, Mumbai, India, Magnesium stearate-Merck Specialities Pvt Ltd, Mumbai, India, Talc-Merck Specialities Pvt Ltd, Mumbai, India.

METHODOLOGY

Analytical method development

Determination of Wavelength

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

Determination of Calibration Curve

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table 8.1 and 8.2) and those concentrations absorbance were found out at required wavelength.

Pre formulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula.

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose
h = Height of the cone, r = Radius of the cone base

Table 7.1: Angle of Repose values (as per USP).

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula
Bulk Density = M / V_o
Where, M = weight of sample
V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:
Tap = M / V
Where, Tap= Tapped Density
M = Weight of sample
V= Tapped volume of powder

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the

bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas.
Carr's Index = [(tap - b) / tap] × 100
Where, b = Bulk Density
Tap = Tapped Density

Table 7.2: Carr's index value (as per USP).

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Formulation development of Tablets
All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 7.3. The tablets were prepared as per the procedure given below and aim is to prolong the release of Doxazosin Mesylate. Total weight of the tablet was considered as 100mg.

Procedure
1) Doxazosin Mesylate and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table 7.3: Formulation composition for tablets.

Ingredients	DM1	DM2	DM3	DM4	DM5	DM6	DM7	DM8	DM9
Doxazosin Mesylate	4	4	4	4	4	4	4	4	4
HPMC K-100	4	8	12	-	-	-	-	-	-
Xanthan gum	-	-	-	4	8	12	-	-	-
Ethyl cellulose	-	-	-	-	-	-	4	8	12
PVP	5	5	5	5	5	5	5	5	5
Lactose	81	77	73	81	77	73	81	77	73
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	2	2	2	2	2	2	2	2	2
Total weight	100	100	100	100	100	100	100	100	100

All the quantities were in mg

RESULTS AND DISCUSSION

The present study was aimed to developing Sustained release tablets of Doxazosin Mesylate using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

8.1. Analytical Method

Graphs of Doxazosin Mesylate were taken in 0.1N HCl and in pH 6.8 phosphate buffer at 245 nm and 245 nm respectively.

Table 8.1: Observations for graph of Doxazosin Mesylate in 0.1N HCl (245nm).

Conc [µg/ml]	Absorbance
0	0
2	0.115
4	0.214
6	0.315
8	0.405
10	0.511

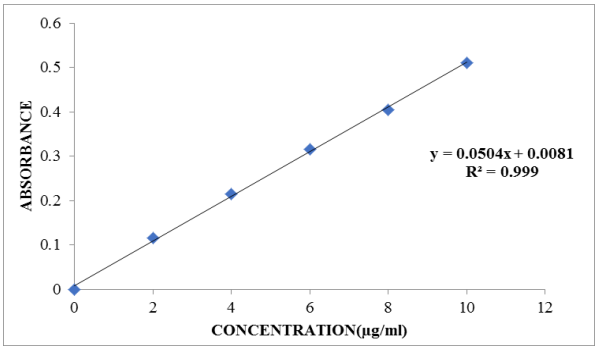

Figure 8.1: Standard graph of Doxazosin Mesylate in 0.1N HCl.

Table 8.2: Observations for graph of Doxazosin Mesylate pH 6.8 phosphate buffer (247nm).

Concentration [µg/ml]	Absorbance
0	0
2	0.109
4	0.222
6	0.331
8	0.438
10	0.547

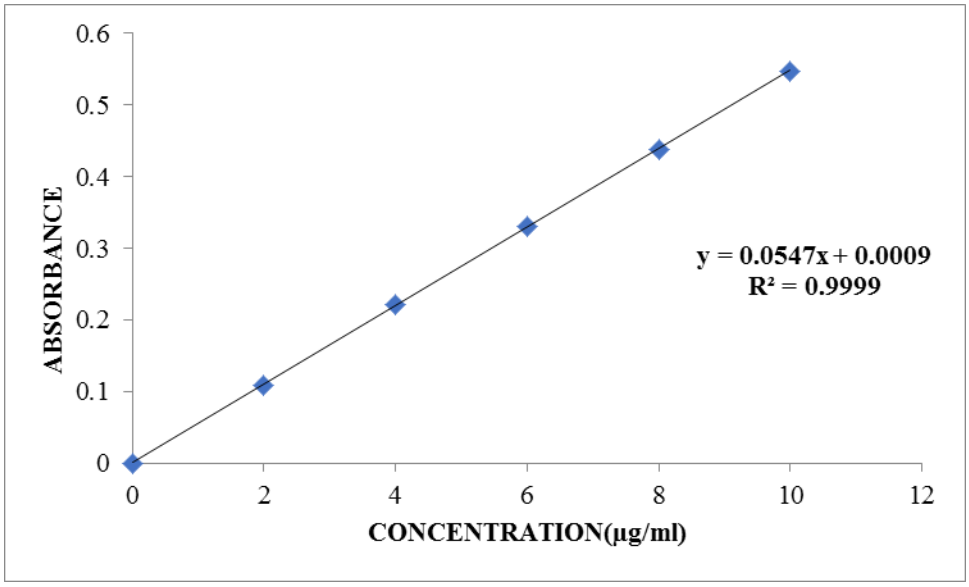

Figure 8.2: Standard graph of Doxazosin Mesylate pH 6.8 phosphate buffer (247nm).

8.2. Preformulation parameters of powder blend

Table 8.3: Pre-formulation parameters of Core blend.

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
DM1	31.68±0.5	0.44±0.145	0.56±0.13	21.42±0.2	1.27±0.1
DM2	22.56±0.4	0.42±0.17	0.52±0.18	19.23±0.1	1.23±0.2
DM3	30.24±0.4	0.48±0.195	0.56±0.1	14.28±0.1	1.16±0.1
DM4	23.85±0.1	0.37±0.160	0.45±0.2	17.77±0.1	1.21±0.1
DM5	25.52±0.4	0.50±0.108	0.63±0.2	20.63±0.2	1.26±0.1
DM6	28.73±0.2	0.52±0.135	0.59±0.2	11.86±0.3	1.13±0.1
DM7	27.58±0.9	0.36±0.096	0.41±0.69	12.19±0.1	1.13±0.1
DM8	24.72±0.2	0.39±0.110	0.42±0.9	7.14±0.2	1.07±0.4
DM9	31.44±0.14	0.42±0.07	0.54±0.10	22.22±0.1	1.28±0.1

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.36±0.096 to 0.52±0.135 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.41±0.69 to 0.63±0.2 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 25 which show that the powder has good flow properties. All the formulations has shown the hausner ratio below 1.333 indicating the powder has good flow properties.

8.3. Quality Control Parameters For tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

8.4. *In vitro* quality control parameters for tablets

Formulation codes	Average weight(mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
DM1	98.12	2.34	0.23	1.85	97.36
DM2	99.35	2.47	0.51	2.15	99.45
DM3	100.22	2.62	0.41	1.89	99.58
DM4	100.08	2.12	0.18	1.72	98.18
DM5	98.37	2.84	0.38	1.92	98.35
DM6	97.59	3.12	0.29	2.22	97.29
DM7	98.76	2.87	0.37	1.93	99.67
DM8	99.31	2.51	0.44	1.88	98.45
DM9	98.53	2.63	0.35	1.76	97.38

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 8.4. The average weight of the tablet is approximately in range of 97.59 to 100.22 mg, so the permissible limit is ±7.5% (>100 mg). 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 Pfizer hardness tester and the data's were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 2.12 to 3.12 kg/cm^2, which was within IP limits.

Thickness

Thickness of three tablets of each batch was checked by using Micrometer and data shown in Table-8.4. The result showed that thickness of the tablet is raging from 1.72 to 2.22mm.

Friability

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 8.4. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Drug content

Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 97.29 - 99.67 %.

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***8.4. In-Vitro* Drug Release Studies**

Table 8.5: Dissolution Data of Doxazosin Mesylate Tablets.

Time(Hrs)	DM1	DM2	DM3	DM4	DM5	DM6	DM7	DM8	DM9
0	0	0	0	0	0	0	0	0	0
0.5	11.88	14.28	08.69	19.17	17.74	15.32	12.58	16.15	14.23
1	15	22.17	12.21	28.23	25.23	26.16	17.55	21.78	19.13
2	19.47	28.89	19.25	37.71	33.58	30.48	24.63	29.23	22.47
3	25.74	36.12	24.45	44.58	39.36	43.54	32.47	35.58	27.98
4	31.11	42.78	28.13	53.31	42.52	49.78	38.52	42.78	36.46
6	38.96	47.29	35.82	57.78	48.58	53.25	45.58	49.27	51.99
7	44.93	51.93	42.72	64.74	56.63	62.89	53.78	56.52	62.14
8	53.47	57.11	49.26	69.25	64.18	75.47	62.58	65.23	67.25
9	59.89	63.48	55.94	75.12	71.99	79.78	73.78	72.59	76.78
10	66.82	69.47	61.86	88.31	77.41	86.33	83.87	85.21	81.47
11	75.75	78.74	72.95	94.48	89.31	91.52	89.19	92.13	85.11
12	82.83	91.98	88.87	99.59	94.14	93.22	97.36	95.44	92.53

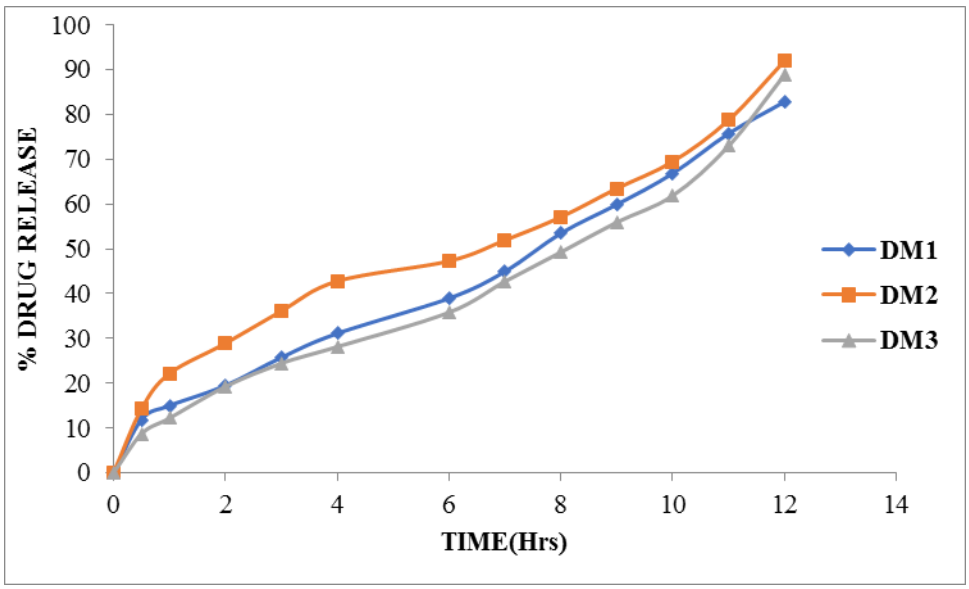

Fig 8.3: Dissolution profile of Doxazosin Mesylate (DM1-DM3 formulations).

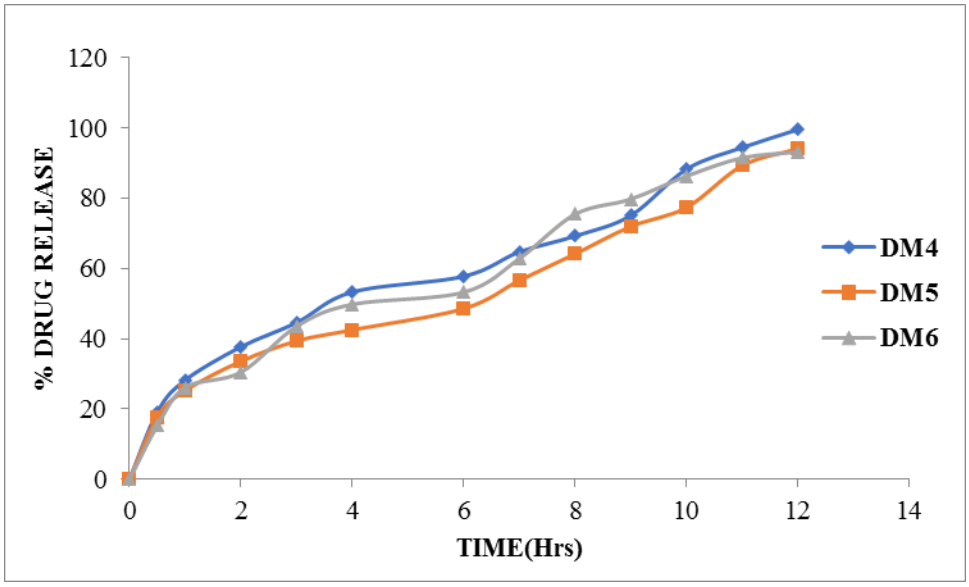

Fig8.4: Dissolution profile of Doxazosin Mesylate (DM4- DM6 formulations).

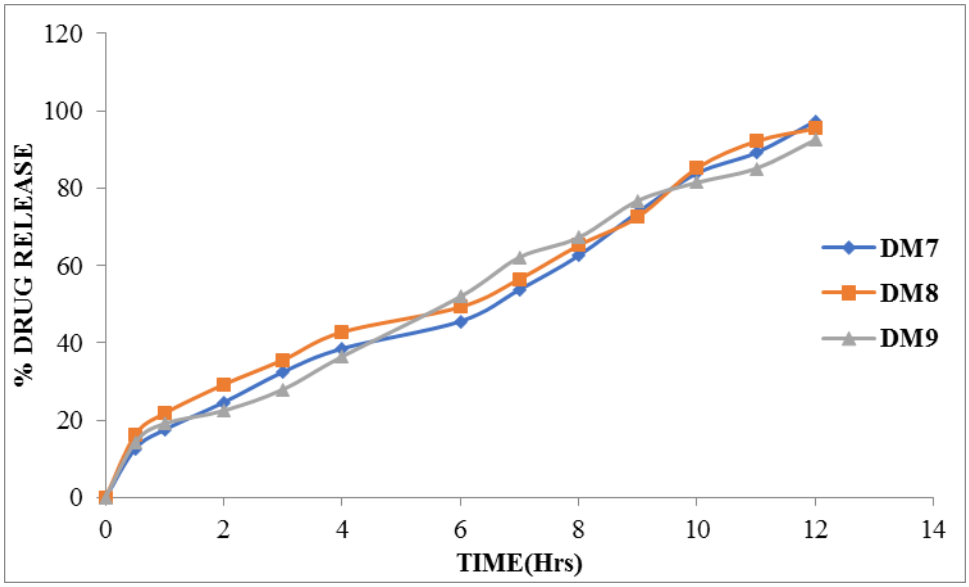

Fig8.4: Dissolution profile of Doxazosin Mesylate (DM7- DM9 formulations).

From the dissolution data it was evident that the formulations prepared with HPMC K-100 as polymer were retard the drug release up to desired time period i.e., 12 hours and showed maximum of (DM2) 91.98% in 12 hours with good retardation.

Formulations prepared with Xanthan gum retarded the drug release in the (DM4Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 99.59% in 12 hours with good retardation but increase the concentration of polymer the release pattern is not uniform.

Formulations prepared with Ethyl cellulose retarded the drug release in the (DM8Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 95.44% in 12 hours with good retardation but increase the concentration of polymer the release pattern is not uniform.

Among all 9 formulations DM4formulation showed good drug release. Among all *in vitro* evaluation parameters DM4 formulation passed all evaluation parameter.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 8.7: Release Rate Kinetics to Dissolution Data

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
19.17	0.5	0.707	1.283	-0.301	1.908	38.340	0.0522	-0.717	80.83	4.642	4.324	0.318
28.23	1	1.000	1.451	0.000	1.856	28.230	0.0354	-0.549	71.77	4.642	4.156	0.486
37.71	2	1.414	1.576	0.301	1.794	18.855	0.0265	-0.424	62.29	4.642	3.964	0.678
44.58	3	1.732	1.649	0.477	1.744	14.860	0.0224	-0.351	55.42	4.642	3.813	0.829
53.31	4	2.000	1.727	0.602	1.669	13.328	0.0188	-0.273	46.69	4.642	3.601	1.041
57.78	5	2.236	1.762	0.699	1.626	11.556	0.0173	-0.238	42.22	4.642	3.482	1.160
64.74	6	2.449	1.811	0.778	1.547	10.790	0.0154	-0.189	35.26	4.642	3.279	1.362
69.25	7	2.646	1.840	0.845	1.488	9.893	0.0144	-0.160	30.75	4.642	3.133	1.509
75.12	8	2.828	1.876	0.903	1.396	9.390	0.0133	-0.124	24.88	4.642	2.919	1.722
88.31	9	3.000	1.946	0.954	1.068	9.812	0.0113	-0.054	11.69	4.642	2.270	2.372
94.48	10	3.162	1.975	1.000	0.742	9.448	0.0106	-0.025	5.52	4.642	1.767	2.874
99.59	11	3.317	1.998	1.041	-0.387	9.054	0.0100	-0.002	0.41	4.642	0.743	3.899
99.23	12	3.464	1.997	1.079	-0.114	8.269	0.0101	-0.003	0.77	4.642	0.917	3.725

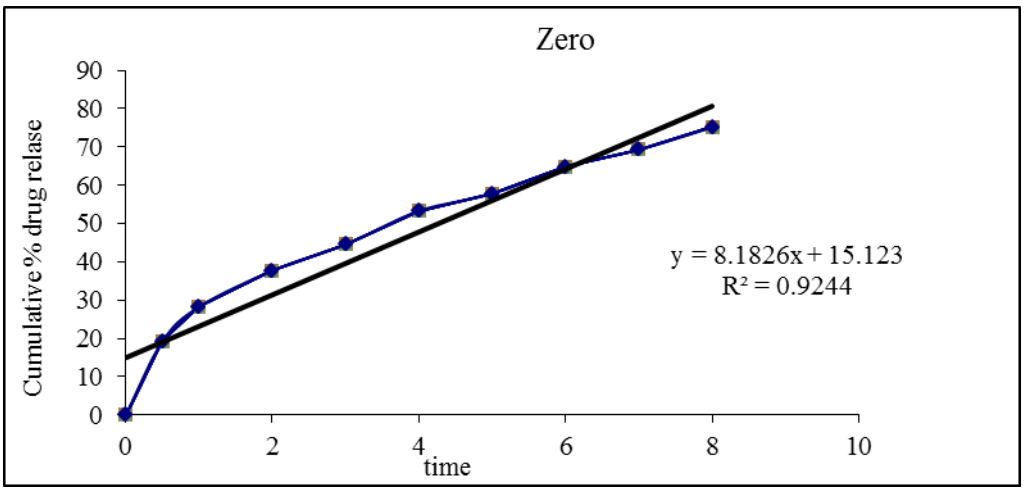

Fig 8.5 : Zero order release kinetics graph.

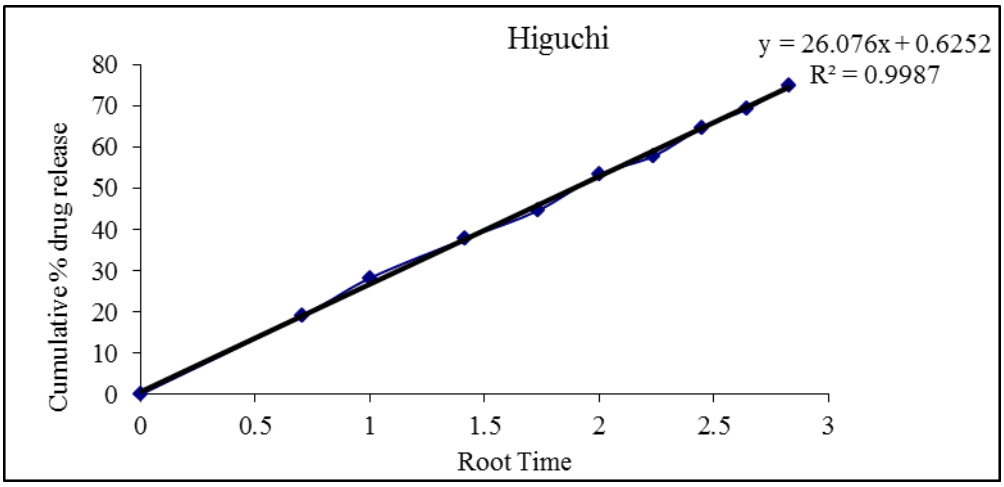

Fig 8.6: Higuchi release kinetics graph.

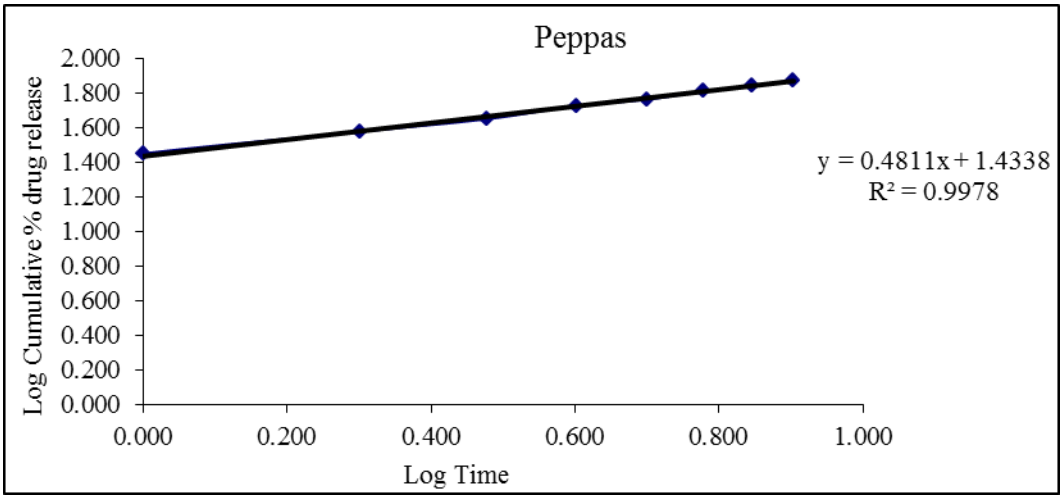

Fig 8.7: Kars mayer peppas graph.

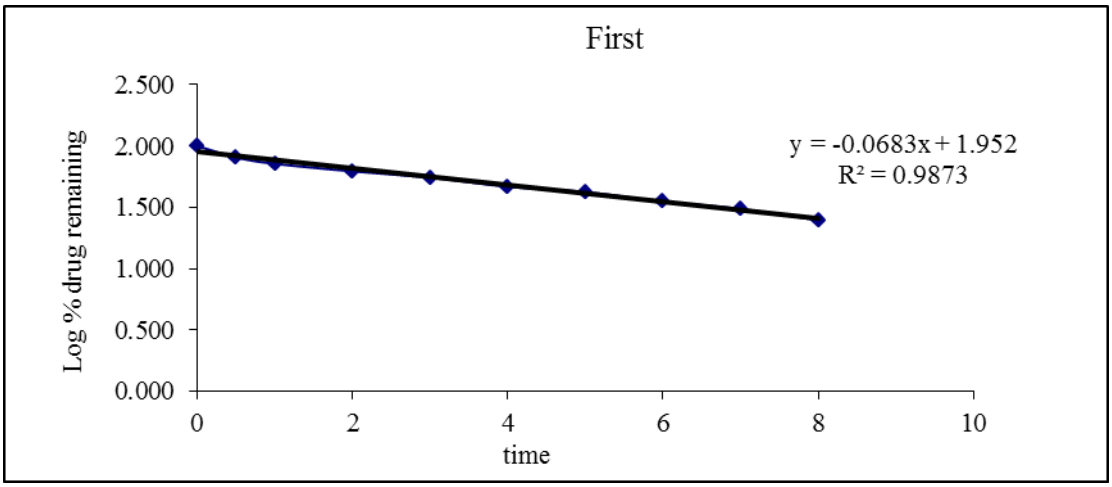

Fig 8.8: First order release kinetics graph.

From the above graphs it was evident that the formulation F9 was followed Peppas release kinetics.

8.6. Drug – Excipient compatability studies

Fourier Transform-Infrared Spectroscopy

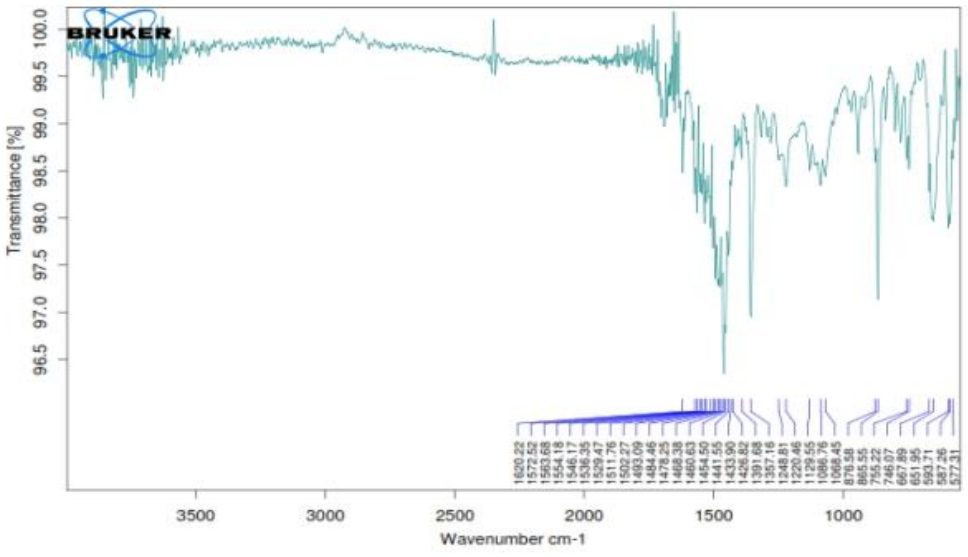

Figure 8.9: FT-TR Spectrum of Doxazosin Mesylate pure drug.

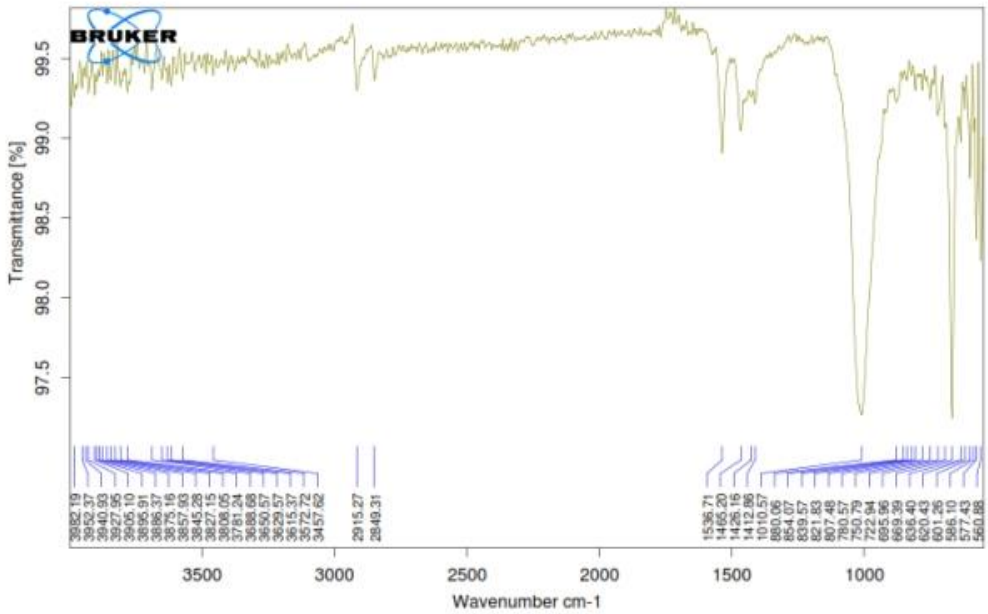

Figure 8.10: FT-IR Spectrum of Optimised Formulation.

From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence they were compatible.

CONCLUSION

Sustained release tablets of Doxazosin Mesylate were prepared using different ratios of HPMC K-100, Xanthan gum and Ethyl cellulose by direct compression method. The results of the present study demonstrates that the all the polymers control the Doxazosin Mesylate release effectively for 12hrs. It is concluded that sustained release of Doxazosin Mesylate over a period of 12hrs was obtained with formulation DM4 containing high amount of Xanthan gum. Sustained release tablets of Doxazosin Mesylate can be expected to reduce the frequency of administration and decrease the dose dependent side effects associated with repeated administration of conventional Doxazosin Mesylate tablets.

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