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Development and Evaluation of Controlled Release Matrix Microspheres of Doxazosin using HPMC and Carbopol

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ABSTARCT

Objective: This study aims to develop and evaluate controlled release matrix microspheres of Doxazosin, a poorly water-soluble antihypertensive drug, to overcome limitations associated with conventional oral dosage forms, including fluctuating plasma levels and frequent dosing.

Methods: Microspheres were formulated using Hydroxypropyl Methylcellulose (HPMC K15) and Carbopol via the emulsion solvent evaporation technique. A series of ten formulations were developed and characterized for drug entrapment efficiency, mean particle size, micromeritic properties, and in-vitro drug release. FTIR and DSC studies were conducted to assess drug–excipient compatibility. Drug release kinetics were analyzed using various mathematical models.

Results: Among all formulations, F7 (HPMC K15: Carbopol = 400:600 mg) exhibited optimal performance, achieving 96% cumulative drug release over 12 hours. The release followed zero-order kinetics with a high correlation coefficient (R^2 = 0.968) and fit best with the Higuchi model (R^2 = 0.995). The Korsmeyer–Peppas model indicated non-Fickian diffusion with an 'n' value of 0.859, suggesting a combination of diffusion and polymer relaxation as the mechanism of release.

Conclusion: The study demonstrates that Doxazosin-loaded matrix microspheres using HPMC and Carbopol can provide sustained and controlled drug release. This delivery approach has the potential to enhance therapeutic efficacy, minimize dosing frequency, and improve patient adherence in hypertension management.

Keyword: Doxazosin, Controlled Release, Matrix Microspheres, HPMC K15,Carbopol 934, Drug Release Kinetics, Non-Fickian Diffusion

INTRODUCTION

Oral route has been the major route of drug delivery for the chronic treatment of many numbers of diseases. This oral route is the major convenient route for drug administration for a being a non-invasive and less cost effective. For poorly soluble drugs, oral route of administration will be major problem[(1)].

Controlled Release Drug Delivery System

Controlled release system means any drug delivery system `that maintains adequate and desired release of drug over an extended period of time. Hydrophilic polymer matrix is widely used for formulating a controlled dosage form. The role of ideal drug delivery system is to provide proper amount of drug at regular time interval and at right site of action to maintain therapeutic range of drug in blood plasma. The IR drug delivery system lacks some features like dose maintenance, controlled release rate and site targeting. The oral controlled drug delivery has some potential advantage like controlled release rate and dose maintenance in plasma. The CR formulations have some swelling polymer, waxes, or both, which controls the release rate. The use of reservoir system is also well known for controlling release rate. Controlled drug delivery is one, which delivers the drug at a predetermined rate, locally or systemically, for a specified period[(2)]. Recently, a new generation of pharmaceutical products, called controlled release drug delivery systems, such as those developed from the osmotic pressure activated drug delivery system, have recently received regulatory approval for marketing, and their pharmaceutical superiority and clinical benefits over the sustained release and immediate release pharmaceutical products have been increased. Controlled release drug administration means not only prolongation of the duration of drug delivery, similar to the objective in sustained release and prolonged release, but the term also implies the predictability and reproducibility of in-vitro dissolution drug release kinetics. To optimize the biopharmaceutical, Pharmacokinetics and Pharmaco-dynamics properties of drug in such a way that it's utility is maximized through reduction in the side effects and cure or control of condition in the shortest possible time by the most suitable route[(3)]. Controlled release denotes that the system is able to provide some actual therapeutic control,

whether this is of a temporal nature, spatial nature, or both. Controlled drug delivery occurs when a polymer is combined with a drug or active agent such that the release from the bulk material is pre-designed[4].

Advantages of controlled release drug delivery system over the conventional dosage form:

- Reduced dosing frequency[5].
- Dose reduction.
- Improved patient compliance.
- Constant level of drug concentration in blood plasma.
- Reduced toxicity due to overdose.
- Reduces the fluctuation of peak valley concentration.
- Night time dosing can be avoided[6].

Limitation of Oral Conventional Dosage Form:

- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary[7].
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication in narrow therapeutic index drug.
- A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition impossible[8].

Introduction of Microspheres

An ideal controlled drug delivery system is the one, which delivers the drug at a predetermined rate, locally or systemically, for a specified period. The concept of micro encapsulation was initially utilized in carbon-less copy papers. More recently, it has received increasing attention in pharmaceutical and biomedical applications. The first research leading to the development of micro-encapsulation procedures for pharmaceuticals was published by Bungenburg de Jong and Kass in 1931 and dealt with the preparation of gelatine spheres and the use of gelatine concentration process for coating[9].

In the late 1930s, Green and co-workers of National cash register co. Dayton, Ohio, developed the gelatine coacervation process. Since then may other coating materials and processes of application have been developed by the pharmaceutical industry for the Microsphere of medicines over the last 25 years, pharmaceutical companies for micro encapsulated drugs have taken out numerous patents. Microsphere is a rapidly expanding technology. As a process, it is a means of applying relatively thin coating to small particles of solids or droplets of liquids and dispersions[10].

Microspheres are defined as 'solid spherical particles containing dispersed drug in either solution or Microcrystalline form.' They are ranging in size from 1 to 1000 micrometer. Microspheres are in strict sense, spherical solid particles. Micro capsules are small particles that contains an active agent as a core material and coating agent as shell[11], at present there is no universally accepted size range that particle must have in order to be classified as microcapsules. However, many workers classify capsules smaller than 1 micrometer as Nano capsules and capsules layer more than 1000 micrometer as macro particles. Commercial microcapsules typically have a diameter between 3-80 micrometer and contain 10-90 weight % cores.

Microsphere is a rapidly expanding technology. It is the process of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions[12]. Microsphere provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection and of controlling the release characteristics or availability of coated materials. Microsphere is receiving considerable attention fundamentally, developmentally and commercially[13]. However, the terms microcapsule and microspheres are often used synonymously. The microspheres are free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature, and ideally having a particle size less than 200 micrometer. Solid biodegradable microcapsules incorporating a drug dispersed or dissolved throughout the particle matrix have the potential for the controlled release of drug[14].

A wide range of core materials have been encapsulated including adhesives, agrochemicals, live cells, active enzymes, flavour fragrances, pharmaceuticals, and inks. Most capsule shell materials are organics, polymers, but fats and waxes are also used. Microcapsules can have a variety of structures some have a spherical geometry with a continuous core region surrounded by a continuous shell as shown. (A) Other has an irregular geometry and contains a number of small droplets as particles of core material as shown. (B) Microcapsules are used in a wide range of oral and injected drug formulation. Encapsulated adhesive resins coated on automotive fasteners are routinely used to assure that such fasteners are firmly set when installed. Microcapsules are also the basis for a number of long acting commercial pesticides and herbicides. Improvement of these products and development of new ones is an ongoing process that involves a large number of development groups globally[15,16].

Merits of Microsphere

Microsphere offers the ability to do the following[17].

- Microsphere change liquid to solid (powder as particles.) E.g. Clofibrate.
- Microsphere separate reactive materials from one another and handle them in a mix. As store them for a long time. E.g. Mix of Aspirin and Chlorfilaramine.
- Microsphere curtails any colour, taste, odour or toxicity generates by core materials. Microsphere protects materials from environment for examples by preventing oxidization. E.g. Vitamin A Palmitate[18].
- Microsphere improves the effective life.
- Microsphere holds a liquid on a flat surface by in effect, changing it to a solid.
- Microsphere controls the releasing conditions. For example, we can control the timing of dissolving, volatilization, colouring, release of smell, mixing and reaction by changing the size of the capsules, the ratio of core materials to shell materials, or the properties of the shell materials, such as strength and permeability or by adding supplementary materials to core or shell materials.
- Microsphere changes the specific gravity[19].
- Microspheres make core materials easy to handle.
- Microspheres solidify tacky materials and increase its fluidity. E.g. thiamine HCL, riboflavin.
- Microspheres are normally used to enhance material stability, reduce adverse or toxic effects as extend material release for different applications in various fields of manufacturing.

Demerits of Microsphere

- Drug entrapment is low because some portion of drug is lost in the dispersion vehicle.
- The industrial scale of microspheres formulation is difficult because to maintain size of microspheres at industry level is difficult.
- The manufacturing of microspheres involves use of solvents, which make the process costly.
- As compared to the extended release tablets and capsules, the manufacturing of microspheres is much more complicated.
- Time consuming process as much time period for required for emulsification, vaporization of solvent and rigidization of microspheres.

Applications of Microspheres

The brief outline of various applications of microsphere is explained as follows:

1. Microspheres in chemotherapy

The most promising application of microspheres is possible to use as carriers for anti- tumour agents. Enhanced endocytic activity and leaky vasculature administrated microspheres. Stealth microspheres are prepared by coating with soluble polyoxyethylene. The accumulation of no stealth microspheres in Reticulo Endothelial System (RES) may also be exploited for cancer chemotherapy[20].

2. Microspheres for DNA Delivery

Microspheres have been recently used as a delivery vehicle for the transfer of plasmid DNA which leads to improve the transfer of plasmid DNA and their stability in the bio- environment. Truong-Le & Co workers (1998) developed a novel system for gene delivery based on the use of DNA-gelatin microspheres/ nanoparticles formed by salt induced complex coacervation of gelatine & plasmid.

3. Fluorescent microspheres

These are made up of polystyrene or poly vinyl toluene, mono disperse system ranging in size from 20nm to 4µm. Preparation of fluorescent microspheres comprising, swelling the polymeric microspheres so that fluorescent dyes may enter the microsphere pores. Unswelling the polymeric microspheres so that the fluorescent dyes become physically entrapped in the pores.

4. Adjuvant effect for vaccines

An adjuvant effect of the microspheres/nanoparticles with either matrix entrapped or surface adsorbed vaccines have been demonstrated in several studies on substances or oral administration. “Kreuter & Co-workers” observed that Poly methyl methacrylate microspheres containing the influenza antigen induced significant antibody response. Oral delivery of antigens with microspheres may be an elegant means of producing an increase Immunoglobulin A (Ig A) antibody response.

5. Microspheres for Ocular delivery

The most applications of drug loaded ophthalmic delivery systems are for glaucoma therapy, especially cholinergic agonists like pilocarpine. The short elimation half life of aqueous eye drops can be extended from a very short time (1-

3 min) to prolonged time (15-20 min) using microspheres which have biodegradable properties e.g. Poly alkyl cyano acrylate.

6. Microspheres for Lymph targeting
The major purpose of lymph targeting is to provide an effective anticancer chemotherapy to prevent the metastasis of tumour cells by accumulating the drug in the regional lymph node. Example: Poly alkyl cyanoacrylate microspheres bearing anticancer drugs for tumour of peritoneal cavity. Poly (lactide-co-glycolide) microspheres for the lymphatic of diagnostic agents.

Types Of Microspheres :
1. Bio adhesive microspheres
2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Polymeric microspheres
i) Biodegradable polymeric microspheres
ii) Synthetic polymeric microspheres

1. Bio adhesive microspheres
Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water-soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc. can be termed as bio adhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application, causes intimate contact with the absorption site, and produces better therapeutic action.

2. Magnetic microspheres
This kind of delivery system is very much important which localises the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are Chitosan, dextran etc. The different types of A. Therapeutic magnetic microspheres used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system. B. Diagnostic microspheres, used for imaging liver metastases and can be used to distinguish bowel loops from other abdominal structures by forming Nano size particles supramagnetic iron oxides.

3. Floating microspheres
In floating types, the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, and the system is found to be floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover, it also reduces chances of dose dumping. It produces prolonged therapeutic effect and therefore reduces dosing frequencies. Drug is given in the form of floating microspheres[(21)].

4. Radioactive microspheres
Radio embolization therapy microspheres sized 10-30 nm are of larger than the diameter of the capillaries and gets tapped in first capillary bed when they come across. They are injected in the arteries that leads them to tumour of interest so all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters.

5. Polymeric microspheres
The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and Synthetic polymeric microspheres.

A. Biodegradable polymeric microspheres
Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and bio adhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium , results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release. However, they provide wide range of application in microsphere-based treatment.

B. Synthetic polymeric microspheres
Synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc. and proved to be safe and biocompatible but the main disadvantage

of these kind of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage[22].

MATERIALS AND METHODS

The materials employed in the formulation were procured from reliable and certified sources to ensure the integrity and reproducibility of the study. Doxazosin was obtained from Stencils Pvt. Ltd., Hyderabad. Carbopol 934 LR, Sodium Lauryl Sulfate, Methanol, and Hydroxypropyl Methylcellulose (HPMC) were sourced from SDFCL, Mumbai, while Dichloromethane was procured from Finar Chemicals Limited, Ahmedabad. All raw materials and excipients were of pharmaceutical or analytical grade and were used without any further purification.

Preformulation Studies

Preformulation studies involves in response to the growing interest in the possible stability and compatibility issues of drug formulations. These studies evolved in order to accommodate the need for fast pharmaceutical screening of the increasing number of drug candidates. These studies include methodologies to characterize the physicochemical properties of the active pharmaceutical ingredients and they provide valuable information essential to select the most appropriate excipients and formulation approach, with least possibility of incompatibility, instability and manufacturing complications.

FORMULATION OF DOXAZOSIN MICROSPHERES

Matrix Microspheres:

All the formulations were prepared by direct compression method using HPMC, polymers in various ratios and other excipients Dichloromethane, methanol, and Carbopol, sodium Lauryl sulfate are used[23].

Procedure:

Accurately weighed dichloromethane and add methanol. To this add HPMC K15 and carbopol in various proportions. To this add drug 500mg of Doxazosin with constant stirring. Inject drop wise in 100ml of 0.2% w/v sodium lauryl sulfate at 250 rpm with constant stirring. A microsphere obtained was washer for 2-3hrs with distilled water and dried at room temperature.

Table: Formulation Trials for Controlled Release Matrix Microspheres of Doxazosin

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)
Doxazosin	500	500	500	500	500	500	500	500	500	500
HPMC K_{15}	1000	900	800	700	600	500	400	300	200	100
Carbopol	10	100	200	300	400	500	600	700	800	900
Dichloromethane	10	10	10	10	10	10	10	10	10	10
Methanol	10	10	10	10	10	10	10	10	10	10
Sodium lauryl sulphate	200	200	200	200	200	200	200	200	200	200
Total weight	1700	1700	1700	1700	1700	1700	1700	1700	1700	1700

Evaluation of Microspheres

The characterization of microcapsule carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. The parameters that are generally evaluated for characterization of microcapsules are:

1. Microsphere size and shape
2. Entrapment efficiency
3. Mean particle size
4. In-Vitro drug release study

1. Microsphere size:

The topological and morphological characteristics of the prepared microspheres were performed by SEM. The microspheres were mounted on metal stubs with double- sided tapes and sputter coated with gold for 90 s at 15 m.

These were then view under scanning electron microscopy using 5 kV. The drug was characterized by particles of spherical shape and heterogeneous size. Drug-loaded microspheres showed regular shape and smooth surface and no free drug was present. Drug-loaded microspheres made with HPMC K15 showed a regular morphology, but also few bubble like structures were present possibly due to Doxazosin were adsorption and not entrapped into the polymeric network.

2. Entrapment efficiency:

Entrapment efficiency was calculated using the following formula reported by Martinac A et al. briefly, 50mg of the prepared microspheres were dissolved in 10ml of methanol and 1ml of the solution was then further diluted with phosphate buffer pH 6.4. The amount of Doxazosin was estimated spectrophotometrically based on absorbance at 225 nm (Shimadzu, UV- 1700).

Drug entrapment efficiency = (Actual drug content/Theoretical drug content) x 100

3. Mean Particle size:

The particle sizes of prepared microspheres were measured by microscopic method. The diameter of 500 microspheres was measured from each batch and the statistical data was obtained. It was found that as concentration of drug increases, the microsphere mean size decreases. The reduction in size of microsphere with changing drug to polymer ratio may be due to a decrease in the viscosity of the internal phase as a result of a decrease in the concentration of solids in the polymer solution.

4. In-vitro drug release:

To find out the in-vitro release the most commonly used techniques is as follows: In vitro release profile of drug from microspheres is examined in Phosphate buffer of pH 6.8 from 3-10 hr. using the rotating basket method specified in USP XX1 AT 100 rpm. Microspheres equivalent to 50mg of drug were suspended in the dissolution medium and the medium was maintained at 37˚C, 5 ml of samples were withdrawn periodically at intervals of half an hour ad same volume of fresh medium was replaced in to the breaker. The concentration of drug released at different time intervals was then determined by measuring the absorbance using spectrophotometer.[7]

Drug Characterization

Bulk Density

Bulk density of a compound various substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring pre sieved granules into a graduated cylinder through a large funnel and measure the volume and weight. The standard results were shown in the table.

$$Bulk\ density = \frac{weight\ of\ granules}{Bulk\ volume\ of\ granules}$$

Tapped Density

Tapped density is determined by placing a graduated cylinder containing a known mass of granules on mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the tapped density may be computed.

The standard results were shown in the table.

$$Tapped\ density = \frac{weight\ of\ granules}{Tapped\ volume\ of\ granules}$$

Carr's Index

Carr's index is measured by using the values of bulk density and tapped density. The following equation is used to find the Carr's index. The standard results were shown in the table.

$$CI = \frac{TD - BD}{TD} \times 100$$

Where, TD = Tapped density
BD = Bulk density

Hausner´s ratio

It is defined as the ratio of the tapped density to bulk density it can also be calculated by using Carr's consolidation index. The standard results were shown in the table.

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

Angle of Repose

Angle of repose is used to determine the flow properties of powders, pellets or granules. The method to find angle of repose is to pour the powder on a conical heap on a level, flat surface and measure the included angle with the horizontal. The standard results were shown in the table.

Tan θ = h/r

Where, h = height of the heap,
r = Radius of the heap

Table no: Scale of Flow ability

Flow Character	Angle of Repose(º)	Hausner's Ratio
Excellent	25 -30	1.00 - 1.11
Good	31 -35	1.12 - 1.18
Fair	36 -40	1.19 - 1.25
Passable	41 -45	1.26 - 1.34
Poor	46 -55	1.35 - 1.45
Very Poor	56 -65	1.46 - 1.59
Very very Poor	> 65	>1.60

Dissolution Test

In vitro drug release from the microspheres was determined using USP- II (paddle) (Labindia) dissolution apparatus. The various parameters for dissolution were given below; the results were mentioned in the respective graphs.

5ml of aliquots of dissolution media were withdrawn each time at suitable time intervals (1, 2, 4, 6, 8, 10, and 12) and replaced with fresh medium. After withdrawing samples were filtered and analyzer after appropriate dilution by using UV Spectrophotometer and concentration was calculated by using standard calibration curve.

Release Kinetics

A. Zero-order model

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation

$$\mathbf{Q_0 - Q_t = K_0 t}$$

Rearrangement of above equation yields

$$\mathbf{Q_t = Q_0 + K_0 t}$$

Where Q_t = the amount of drug dissolved in time t,

Q_0 = the initial amount of drug in the solution,
K_0 = is the zero order release constant, expressed in units of concentration/time.
To study the release kinetics, the data obtained from in vitro drug release studies were plotted as cumulative amount of drug released versus time.

Application: This relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix microspheres with low soluble drugs in coated forms, osmotic forms etc.

B. First order model

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by the equation,

dc / dt = Kc

Where, K is first order rate constant expressed in units of time

Above equation can be expressed as:

$$\log C = \log C_0 - Kt / 2.303$$

Where, C_0 = initial concentration of drug, k is the first order rate constant,
t = the time

The data obtained was plotted as log cumulative percentage of drug remaining vs. time in which would yield a straight line with a slope of -K/2.303.

Application: This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices.

C. Hixson-Crowell model
Hixson and Crowell recognized that the particles regular area is proportional to the cube root of its volume. They derived the equation

$$W_0^{1/3} - Wt^{1/3} = k\,t$$

Where, W_0 = initial amount of drug in the pharmaceutical dosage form,
Wt = remaining amount of drug in the pharmaceutical dosage form at time
K (kappa) = constant incorporating the surface and volume relation.

The equation describes the release from systems where there is a change in surface area and diameter of particles or microspheres. To study the release kinetics, data obtained from in vitro drug release studies were plotted as cube root of drug percentage remaining versus time and it was shown.

Application: This expression applies to pharmaceutical dosage form such as microspheres, where the dissolution occurs in planes that are parallel to the drug surface if the microspheres diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time.

D. Higuchi Model
A large number of modified release dosage form contain some sort of matrix system. In such instances, the drug dissolves from matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion controlled). In Higuchi model a plot of cumulative percent drug released versus square root of time is linear was shown. Equation is given by,

$$Q = K_2\,t^{1/2}$$

Where, K_2 is rate constant
t is time

E. Korsemeyer Peppas model
Korsemeyer derived a simple relationship which describes drug release from a polymeric system equation. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsemeyer Peppas model. A plot of log % drug release versus log t was shown.

The equation is given by

$$Q/\,Q_0 = k\,t^n$$

Where, $Q/\,Q_0$ = fraction of drug released at time t

n = release exponent indicates mechanism of release

The mechanism of drug release based on n values of peppas as shown.

Table: Mechanism of Drug Release Based on N Value of Peppas

Mechanism of release	n value
Non-fickian diffusion	0.45-8
Fickian	Above 8
Zero order	=1
Super case transport II	Above 1

The r^2 values for release kinetics and n values Korsmeyer-peppas is mentioned.

RESULTS AND DISCUSSION

Drug Excipient Incompatibility Studies
FTIR Studies:

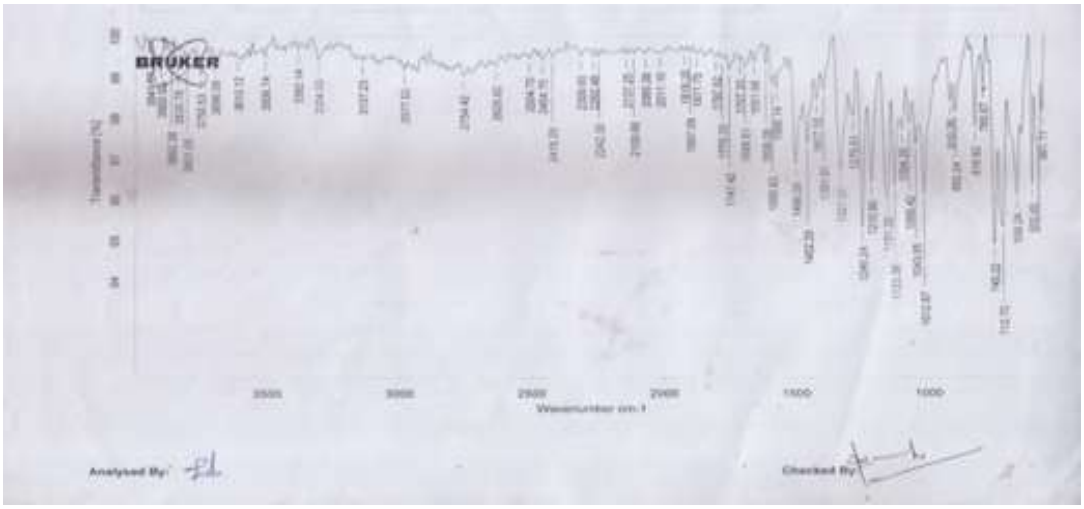

Figure: FTIR Studies for drug (Doxazosin)

Table: Characteristic bands and their corresponding possible functional groups for pure drug

S.No.	Functional group	Range	Absorved value
1	C=C STRECHING	1700-1500	1651.68
2	C-C BENDING	1300-1100	1151.30
3	C-O STRECHING	1210-1320	1246.24
4	C-N STRECHING	1080-1360	1327.07
5	N-H STRECHING	3300-3500	3304.93
6	S-N BENDING	700-723	712.70
7	S=O STRECHING	1300-1150	1123.38
8	C-S STRECHING	710-570	659.24
9	C-H STRECHING	2900-3100	2977.53

All the values are within the standard range hence the drug is in pure form

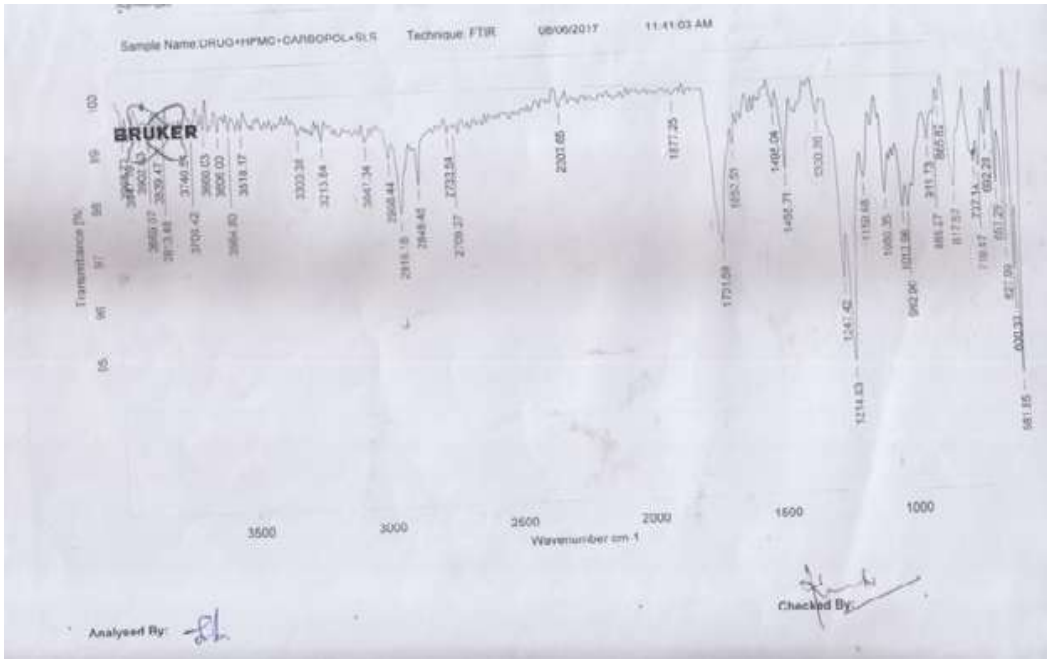

Figure: FTIR Studies for drug + excipients

Table : Charecteristics bands and their corresponding possible functional group for pure drug in mixture of drug + HPMC + SLS + Carbopol

Formulation code	Zero order		First order		Higuchi method		Korsmeyer-peppas		HixsonCrowell method		Mechanism of drug release
	R^2	Slope	R^2	Slope	R^2	Slope	R^2	Slope	R^2	Slope	
F-1	0.959	15.094	0.932	0.317	0.984	53.42	0.986	0.841	0.916	0.341	Non fickian
F-2	0.913	13.013	0.982	0.161	0.963	46.72	0.970	0.761	0.868	0.310	Non fickian
F-3	0.915	13.486	0.978	0.232	0.979	50.26	0.980	0.786	0.880	0.310	Non fickian
F-4	0.897	10.558	0.988	0.168	0.958	42.63	0.964	0.750	0.839	0.245	Non fickian
F-5	0.891	10.794	0.982	0.170	0.959	43.74	0.946	0.839	0.491	0.120	Non fickian
F-6	0.865	8.255	0.987	0.115	0.944	36.66	0.927	0.812	0.761	0.203	Non fickian
F-7	0.968	7.529	0.921	0.108	0.995	34.85	0.981	0.859	0.880	0.192	Non fickian
F-8	0.945	7.020	0.914	0.057	0.971	32.50	0.902	1.739	0.790	0.268	Super case II transport
F-9	0.975	7.352	0.955	0.070	0.985	28.87	0.988	0.755	0.921	0.220	Non fickian
F-10	0.965	7.205	0.895	0.036	0.994	28.41	0.989	0.660	0.699	0.187	Non fickian

S.No.	Functional group	Range	Absorved value
1	C=C STRECHING	1700-1500	1652.5
2	C-C BENDING	1300-1100	1159.68
3	C-O STRECHING	1210-1320	1247.42
4	C-N STRECHING	1080-360	1330.26
5	N-H STRECHING	3300-3500	3303.38
6	S-N BENDING	700-723	719.47
7	S=O STRECHING	1300-1100	1214.83
8	C-S STRECHING	710-570	657.29
9	C-H STRECHING	2900-3100	2977.53

DSC Studies

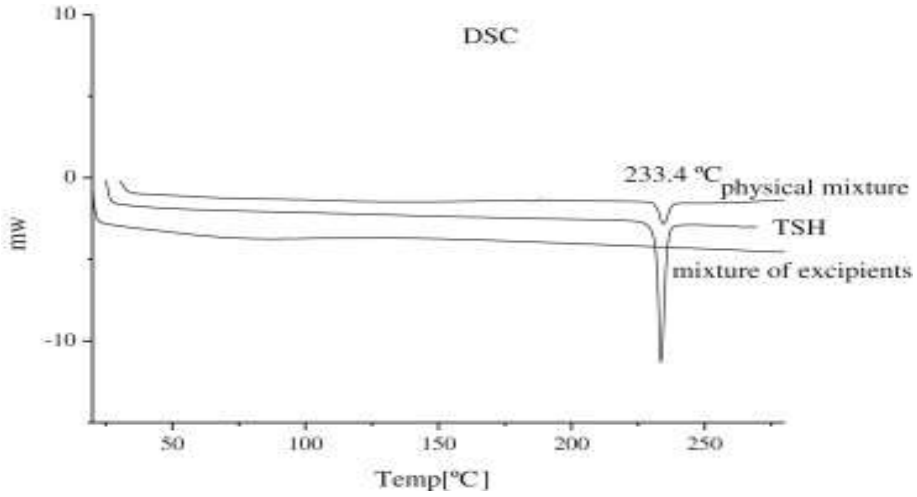

Figure: DSC Studies

Doxazosin HCl shows endothermic in DSC studies the standard melting point of the pure drug is 228ºc same was seen in DSC thermo gram in the presence of various excipients hence there is no interaction between drug and excipients.

Dissolution Studies

Table: In-vitro cumulative percentage drug release

Time (hrs)	Cumulative Percentage (%) Drug Release(Avg±SD) n=3									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	25	24	25	21	17	14	11	1	14	18
2	40	40	44	39	35	32	24	4	23	26
3	64	63	65	54	60	52	33	20	36	39
4	81	78	82	76	73	69	49	39	42	46
6	98	87	94	89	84	76	61	47	51	57
8	98	87	94	94	95	88	76	53	68	69
10	98	87	94	94	95	92	84	69	68	69
12	98	87	94	94	95	-2	96	78	69	69

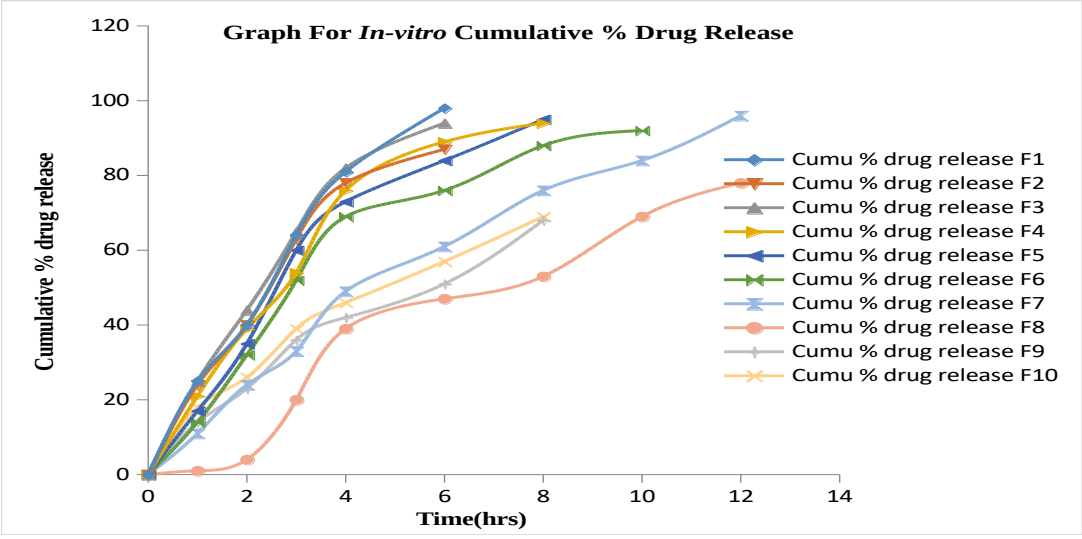

Fig Dissolution Studies

Cumulative percentage drug release for formulation F7 is highest in 12hrs and lowest for formulation F9.

Formulation F1, F2, F3,F 4, F5,F6 these are follows zero order and F7 is showingzero order higuchi model R^2 is 0.999 it says the release due to the swellable polymer and F1, F2,F3,F4,F5... etc, follows non fickian diffusion only F8 follows case2.

CONCLUSION

It is imperative to summarize the findings of the dissertation entitled "Formulation and In-Vitro Evaluation of controlled release Matrix Microspheres of Doxazosin". Prior to the development of dosage form, all the fundamental physical and chemical properties of the drug molecule are evaluated and the results were found satisfactory. This information will dictate the subsequent events and possible approaches in formulation development selection of suitable process, selection of the correct technical grade of excipients. Preformulation studies were carried out and it was concluded from the observations that the drug was compatible with the studied excipients.

The formulation was characterized for various properties of the dosage forms such as dissolution and other physical properties. From the above studies among all the formulations, it has been concluded that formulation F7 containing HPMC k15: Carbopol in the ratio of 400:600 mg has shown highest percentage of drug release i.e., 96% in 12 hours, in controlled manner, following zero order drug release 0.968 with diffusion coefficient of 0.859 that indicates non-fickian diffusion.

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