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PREPARATION AND EVALUATION OF MATRIX NANOSPHERES LOADED WITH SILADOSIN FOR CONTROLLED RELEASE

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ABSTRACT
A selective alpha-1 adrenoceptor antagonist, silodosin, is used for the treatment of benign prostatic hyperplasia. However, because of silodosin's short half-life, the drug needs to be administered frequently, resulting in patients not adhering to the treatment plan. During the present study, the aim was to formulate and evaluate controlled release matrix microspheres of silodosin in order to improve the therapeutic efficacy of the drug and the compliance of the patient. We characterized the particle size, the encapsulation efficiency, and the release of drugs from the prepared microspheres in vitro in order to evaluate their efficacy. Upon analysis of the particle size distribution, it was found that the microspheres had an average size range of m and were uniformly spherical. By scanning electron microscopy (SEM), we were able to observe that the microspheres had a smooth surface morphology. The results of this study suggest that the controlled release matrix microspheres of silodosin are effective in prolonging release time, reducing the frequency of dosing, and possibly improving patient compliance by prolonging the release of the drug. Silodosin could be significantly enhanced in its effectiveness if a controlled release formulation is developed, and this study provides a promising approach towards the development of such a formulation.

Key words: Oral, Microspheres, Controlled Release, Siladosin.

INTRODUCTION

Traditionally, oral drug delivery has been the most effective method for treating a wide variety of chronic diseases. As a non-invasive and less cost-effective route for drug administration, the oral route is the most convenient option for administration. The oral route of administration will present a significant problem for poorly soluble drugs.

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.

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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 [1].

introduction of Microspheres [2]

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 microencapsulation was initially utilized in carbonless copy papers. More recently, it has received increasing attention in pharmaceutical and biomedical applications. Microsphere of medicines over the last 25 years, pharmaceutical companies for microencapsulated 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.

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. Microcapsules are small particles that contains an active agent as a core material and coating agent as shell, 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 [3].

Fundamental Consideration [4]

Microsphere often involves a basic understanding of the general properties of microcapsules, such as the nature of the core and coating materials, the stability and release characteristics of the coated materials and the microsphere methods. The intended physical characters of the encapsulated product and the intended use of the final product must also be considered [5].

A. Core material
B. Coating material
C. Selected stability, release and other properties
D. Physical character of the final product

Types of microspheres :

- Bio adhesive microspheres
- Magnetic microspheres
- Floating microspheres
- Radioactive microspheres
- Polymeric microspheres
  A. Biodegradable polymeric microspheres
  B. Synthetic polymeric microspheres [7]

Methods of Preparation [8]

Solvent removed technique

A. Emulsion – solvent evaporation technique
   - Oil in water (o/w) emulsion solvent evaporation
   - Water in oil (w/o) emulation solvent evaporation
   - Water in oil in water oil water (W/O/W) emulsion solvent evaporation
B. Emulsion solvent extraction
C. Emulsion solvent diffusion

1. Coacervation and Phase Separation Technique

- By temperature change
- By incompatible polymer addition
- By non solvent addition
- By salt addition
- By polymer-polymer interaction.
- By solvent evaporation

2. Cross – linking technique

- Chemical cross linking
- Thermal cross linking

3. To form Polymerization Technique

- Normal polymerization
- Vinyl polymerization
- Interfacial polymerization

4. Spray drying and spray congealing
5. Freeze drying technique
6. Precipitation technique
7. Multi orifice centrifugal process
8. Pan coating
9. Air suspension coating
10. Melt dispersion technique

MATERIALS AND METHODS

MATERIALS USED

Siladosin, Carbopol 934 LR, Sodium Lauryl Sulfate

Equipements Used

Analytical balance, Digital pH meter, Hot air oven, Mechanical stirrer, Fourier transform infra-red spectrophotometer(FTIR), Magnetic stirrer, Sonicator (ultra-sonic Cleaner), Dissolution tester (USP), Double beam UV- Spectrophotometer.

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.

Estimation of λmax Estimation of Siladosin:

A spectrophotometric method based on the measurement of absorbance at 224 nm in 0.1N HCl was used in the present study for the estimation of Siladosin. The parameters are mentioned and the respective graph.
Reagents:

Preparation of 0.1N HCl:

8.5ml of concentrated HCl was taken in a volumetric flask and it was made up to 1000ml with distilled water.

Standard solution:

100mg of Siladosin pure drug was dissolved in 100ml of 0.1 N HCl (stock solution- 1000µg/ml), from this 10ml of solution was taken and the volume was adjusted to 100ml with 0.1 N HCl (100µg/ml).

Estimation of Siladosin 6.8 pH Buffer:

A spectrophotometric method based on the measurement of absorbance at 224 nm in 6.8 pH was used in the present study for the estimation of Siladosin. The parameters are mentioned and the respective graph.

Standard solution:

100mg of Siladosin pure drug was dissolved in 100ml of 6.8 pH (stock solution- 1000µg/ml), from this 10ml of solution was taken and the volume was adjusted to 100ml with 6.8 pH (100µg/ml).

Compatibility Studies

Differential scanning calorimetric (DSC) studies

Interaction studies were carried out to investigate any interaction between drug and polymer as well as other excipients interactions is accelerated stability studies, but it is time consuming and tedious. DSC is fast and reliable method to screen Drug-Excipients compatibility and provide maximum information about the possible interactions.

In DSC, the sample and the reference are thermally isolated from each other and each is fitted with its own temperature sensitizer and a heater. A signal proportional to the differences in power supplied to the sample and reference material is plotted against the sample temperature, whenever, there is any change in the sample due to heating, more power is supplied to keep the temperature of the reference and the sample same. This difference in power supplied between the reference and the sample is recorded as a peak. The area under the curve (AUC) obtained from a DSC scan is proportional to the enthalpy change, which is recorded as a positive peak exothermic or a negative peak (endothermic). To check potential, the drug and excipients are mixed and scanned at a heating rate of 10˚C per minute under an inert atmosphere of nitrogen. The temperature range selected must encompass all thermal features of the drug and excipients like melting point, desolation, polymorphism and decomposition. An interaction is concluded by elimination of endothermic or exothermic peaks, appearance of new peak(s), changes in peak shape and its onset, melting point and relative peak height. The resultant peaks for compatibility studies.

DSC Interpretation

The DSC thermo grams Siladosin exhibited an endothermic in the regions of 226˚C respectively corresponding with their melting points. However, an endothermic peak corresponding with the melting of Siladosin absent in the DSC of pure drug with excipients. By comparing the thermo grams of pure drug, pure drug with placebo we can say that the drug is compatible with the given excipients. The thermo grams of drugs, drug with placebo [6].

Formulation of Siladosin 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.

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:

- Microsphere size and shape
- Entrapment efficiency
- Mean particle size
- 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 (JEOL, JSM-5610 LV, Japan) 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 Siladosin 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 Siladosin was estimated spectrophotometrically based on absorbance at 225 nm (Shimadzu, UV- 1700).

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. DRUG

Characterization

Bulk Density

Bulk density of a compound various substantially with the method of crystallization, milling or formulation. Bulk density is determined.

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.

Carr's Index

Carr's index is measured by using the values of bulk density and tapped 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.

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.

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.

Dissolution Medium of 0.1N HCL

Apparatus - USP-II, Paddle Method Dissolution Medium - 0.1N HCl (First 2 hrs)
RPM - 50
Sampling intervals - 1, 2, 4, 6, 8, 10, and 12hrs.
Temperature - 37±0.5ºC

Dissolution Medium of 6.8 pH

Apparatus - USP-II, Paddle Method Dissolution Medium - 6.8 pH (up to 12 hrs) RPM - 50
Sampling intervals - 1, 2, 4, 6, 8, 10, and 12hrs.
Temperature - 37±0.5ºC

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 [9, 10].

Release Kinetics

The r^2 values for release kinetics and n values Korsmeyer-peppas is mentioned [11-14].

Table 1: 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

Table 2: Physical Characterization of Siladosin

Physical Properties	Siladosin
Physical appearance	white in color, amorphous in nature
Angle of Repose(º)	28.59
Bulk Density (gm/ml)	0.335
Tapped Density (gm/ml)	0.487
Hausner´s ratio	1.065
Carr's consolidation index (%)	9.684

Table 3: Characterization of Siladosin microspheres

S. No.	Formulation code	Mean particle size	% Entrapment efficiency
1	F1	11.26±1.19	79.33±1.07
2	F2	214.26±1.15	85.35±0.63
3	F3	30.76±1.24	89.82±0.85
4	F4	151.32±0.82	68.03±2.08
5	F5	73.76±1.26	74.24±0.64
6	F6	66.76±1.92	80.15±1.82
7	F7	155.32±0.63	74.23±0.62
8	F8	177.74±0.35	80.62±0.57
9	F9	89.44±0.23	85.28±0.66
10	F10	121.26±1.22	82.424±1.81

Table 4: In-vitro drug release kinetic studies

Formulation code	Zero order		First order		Higuchi		Korsmeyer-peppas		Hixson-Crowell 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

Figure 1: Formulation 7

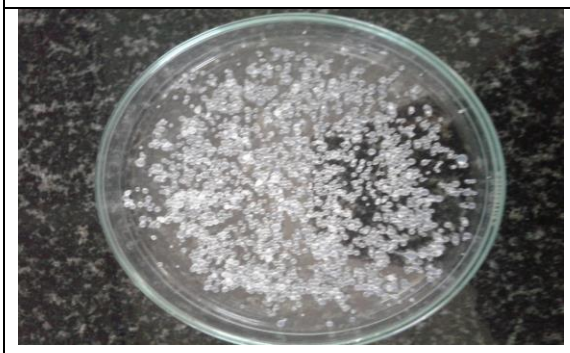


Figure 2: Calibration curve of Tamsulosin in 0.1N HCl at 224nm

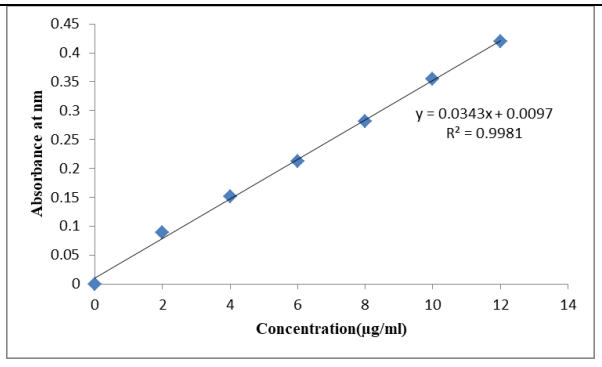


Figure 3: Calibration curve of pH 6.8 buffer

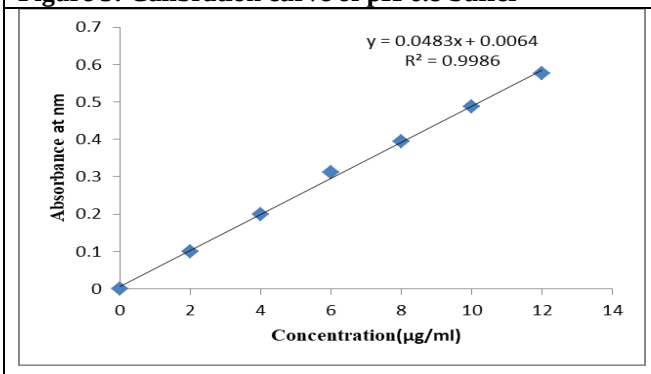


Figure 4: FTIR Studies for drug (Siladosin)

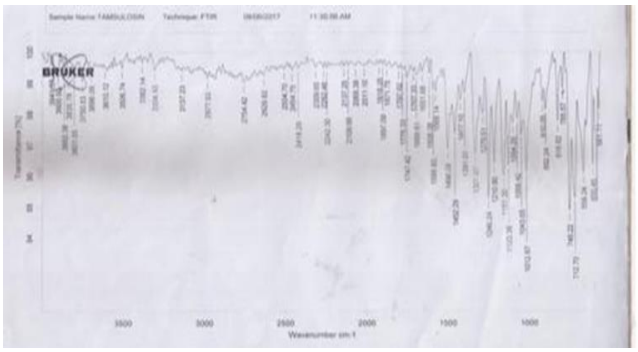


Figure 5: FTIR Studies for drug + excipients

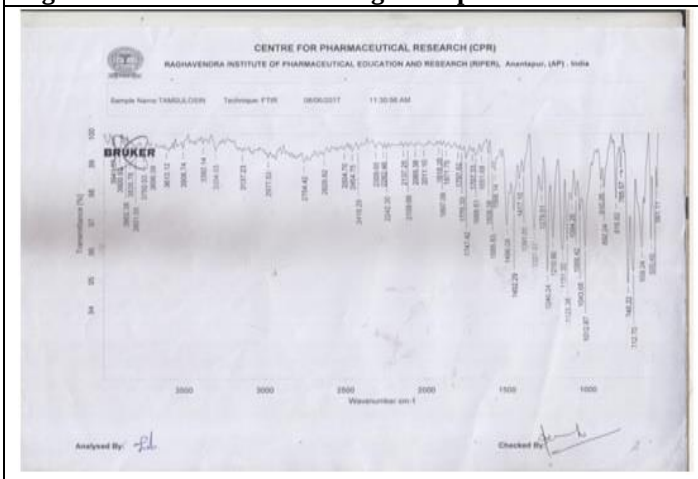


Figure 6: DSC Studies

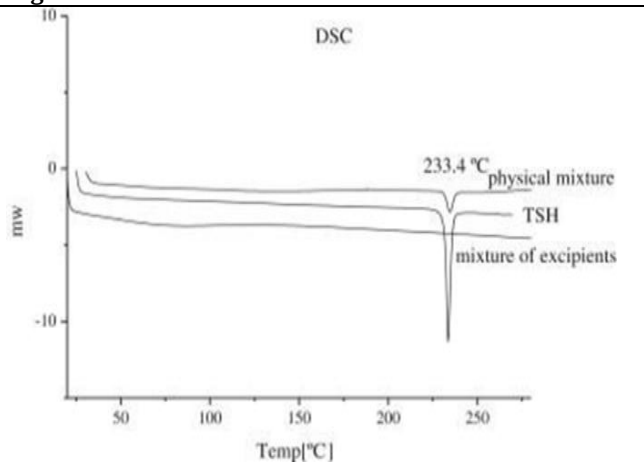


Figure 7: Surface and size of the microspheres are uniform 100µm The drug was characterized by particles of spherical shape and heterogeneous size

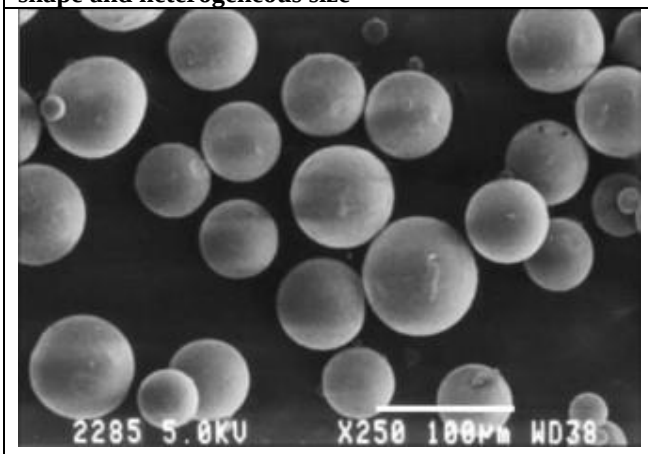
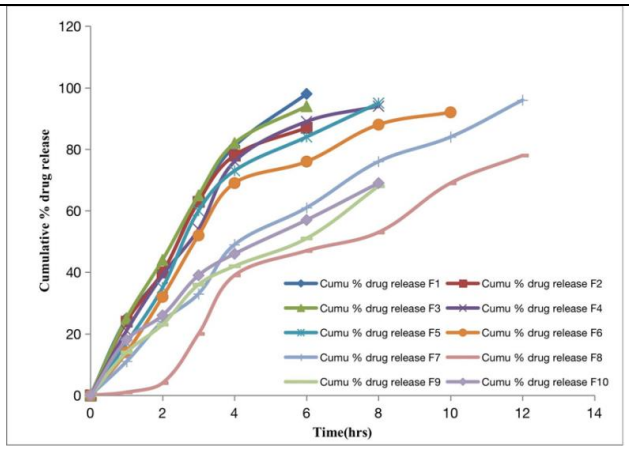


Figure 8: Dissolution Studies



RESULTS AND DISCUSSION

In the present study, Formulation and In-vitro Evaluation of Siladosin controlled release matrix microspheres were prepared and evaluated. The formulations of Siladosin were prepared by solvent evaporation method using HPMC K15 and Carbopol as release retarding agents in different ratios employing Sodium lauryl sulphate and Dichloro methane and Methanol are used. The drug- excipients interactions studies were carried out using ATR and DSC. These results showed that the drug was compatible with all excipients used in the formulation. Characterization for Siladosin was

done on the following parameters: physical appearance, melting point, hygroscopicity, Partition coefficient. The results of the solubility studies were given in the table. Pre compression and Post compression studies of blend and formulations and dissolution profile for individual trial are mentioned in the tables. The standard graph of Siladosin in 0.1N hydrochloric acid was developed by using UV spectrophotometer at 224nm. Regression coefficient obtained was 0.999.

PREFORMULATION

Calibration Curve of Siladosin in 0.1 N HCl at 224 nm.

From the above calibration curve it shows that it follows beer lamberts law, slope was found to be 0.034 with regression of 0.998.

Calibration Curve of Siladosin in 6.8 pH at 224nm.

From the above calibration curve it shows that it follows beer lamberts law, slope was found to be 0.034 with regression of 0.998.

Drug excipient incompatibility studies.

Siladosin 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.

Scanning Electron Microscopy

Mean particle size more for formulation F2 (214.26), least for formulation F3. Percentage entrapment efficiency is ranging between 68 to 85 highest in formulation F3.

Dissolution studies

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

CONCLUSION

It is imperative to summarize the findings of the dissertation entitled “Formulation and In-Vitro Evaluation of controlled release Matrix Microspheres of Siladosin”. 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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