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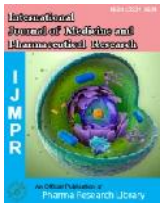

Research Article **Open Access**

Formulation and Evaluation of Sustained Release Tablets of Buclizine Hydrochloride

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A B S T R A C T

Sustained release, sustained action, controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug therapy systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. In the present study an attempt was made to prepare sustained release tablets of buclizine hydrochloride. Buclizine hydrochloride is anti-histaminic agent or anti emetic drug and used to prevent to treat nausea, vomiting and dizziness caused by motion sickness with less halflife and bioavailability. To maintain the therapeutic drug concentration in systemic circulation for longer time and to improve bioavailability, nine formulations of buclizine hydrochloride (F1 to F9) were prepared by wet granulation method using different polymers like HPMC and Ethyl cellulose in varying ratios. All the formulations were evaluated for various physicochemical properties and found to be within the limits, in-vitro dissolution studies indicated that F9 formulation shows better drug release and the mechanism of drug release follows zero order with non-fickian diffusion transport.

Keywords: Sustained release, Anti-Histaminic agent, buclizine hydrochloride, *In-vitro* dissolution

A R T I C L E I N F O

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1. Introduction

Sustained release describes the release of drug substance from a dosage form or delivery system over an extended period of time. The basic goal of this system is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal [1]. Sustained release, sustained action, controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug therapy systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose [2-5]. In the case of injectable dosage forms, this period is measured in hours and critically depends on the residence time of the dosage form in the gastrointestinal tract.

The concept of sustained release drug delivery has been explored for the delivery of drugs for prolong period of time for the past few years[6]. This type of drug delivery has proven to provide a solution to several problems encountered in the repeated administration of conventional dosage forms. Utilizing the concept of incorporating drug in to the polymer system and extend the drug release for prolong period of time, an attempt was made to design and evaluate sustained release tablets of buclizine hydrochloride.

Buclizine hydrochloride is Anti-histamine and Anti-cholinergic of the piperazine derivative family it is considered to be an Anti-emetic similar to meclizine hydrochloride. The aim of this study was to Develop sustained release tablets of buclizine hydrochloride using polymers and evaluate the formulations using to the physic chemical parameters to maintain the therapeutic drug concentration in systemic circulation for longer time. Buclizine hydrochloride which acts to block the histamine receptors in the following centre and thus reduce activity along these pathways, furthermore since buclizine hydrochloride processes anti cholinergic properties as well the muscarinic receptors are similarly blocked

2. Materials and Methods

Materials

Buclizine hydrochloride was obtained from KP LABS, Hyderabad. HPMC, Ethyl cellulose, Starch pregelatinized, were purchased from Drugs India Pvt. Ltd (India). All the remaining ingredients and chemicals utilized were of analytical grade.

Methods

Formulation of Sustained Release Tablets

Preparation of Buclizine hydrochloride sustained released tablets by wet granulation method by using the compositions as mentioned in the table given below

Preparation of tablets by wet granulation method

Mixing:

Buclizine hydrochloride, HPMCk 100M, Ethyl cellulose all the ingredients where taken in required quantities.

Preparation of starch solution:

Starch was dissolved in the required quantity of water and boils the solution for 10min after this starch solution added.

Addition:

The above solution was added to the drug substance for 2-3 mins. and after this substance passed through the 40 no mesh. Finally to obtained the granules.

Drying:

The wet mass was dried in a hot air oven at 45-50^0 C for 30 mins ofter to abtained the dry granules. talc and magnesium stearate mix this dry granules.

Compression:

Blended material was loaded in a hopper and compresses the powder in to tablets by using tablet compressing machine filled with biconvex punches

Evaluation

Construction of Calibration Curve:

The Calibration curve of buclizine hydrochloride was constructed by preparing three stock solutions.

Preparation of 0.1M HCL1.2 pH:

Accurately measured 8.5ml of concentrated HCl was added to 1000ml to make 0.1M HCl. The resulting solution pH was measured by Ph meter and it was recorded as 1.2pH

Preparation of stock solution I

Accurately weighed 100mg of Buclizine Hydrochloride was dissolved in 10ml of methanol taken in volumetric flask and volume was made up to 100ml with 0.1M HCl. This is called stock solution I.It contains 1000µg/ ml of buclizine hydrochloride.

Preparation of stock solution II

From the stock solution I 10ml of solution was pipette out and made up to the 100ml with the 0.1M HCl. This is called stock solution II. It contains 100µg / ml of Buclizine Hydrochloride.

Preparation of stock solution III

From the stock solution II 10ml of solution was pipette out and made up to the 50ml with the M HCl. This is called stock solution III .It contains 10µg/ml of Buclizine hydrochloride.

Preparation of aliquots

The aliquots were prepared from stock solution III whose concentration ranging from 1 to 2 µg /ml. The absorbance was measured at 225nm by using UV spectrophotometer against the blank.

Evaluation of Granules

Buclizine hydrochloride sustained release granules used for the formulation of Buclizine hydrochloride sustained release tablets were evaluated for derived and flow properties before preparing formulations. Before formulation of drug substances in to a dosage form, it is essential that drug and polymers should be chemically and physically characterized. Preformulation studies gives the information needed to define the nature of the drug substance and provide a frame work for the drug combination with pharmaceutical excipients in the manufacture of a dosage form.

2.1. Pre-Compression parameters [8-10]

2.1.1. Bulk Density:

It was determined by pouring pre-sieved drug excipients blend in to a graduated cylinder and measuring the volume and weight as it is. It is generally

Expressed in g/ml and is given by,

Db= M/VO

Where,

M is the mass of powder and V_O is the Bulk volume of the powder.

2.1.2. Tapped density

It was determined by placing a graduated cylinder, containing a known mass of drug –excipients blend, on mechanical tapping apparatus.

DT = M/VT

Where,

M is the mass of powder and VT Is the tapped volume of the powder.

The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ ml.

2.2. Powder flow properties:

2.2.1. Angle of repose

This is the maximum angle possible between the surface of the pile or powder and horizontal plane. Angle of repose was determined by using funnel method. The frictional forces in the lose powder can be measured by Angle of repose. The tangent of Angle of repose is equal to the coefficient friction between the particles.

$\Theta = \tan^{-1}(h/r)$

Where,

Θ is the angle of repose, h is the height in cm and r is the radius in cm.

2.2.2. Compressibility index

It is an important measure that can be obtained from the bulk and tapped densities. A material having values less than 20 to30% is defined as the free flowing material. Based on the apparent bulk density and tapped density, percentage compressibility of the bulk drug was determined by using the following formula.

$I = DT - Db / DT \times 100$

Where,

I is the Compressibility index,

D_T is the tapped density of the powder; D_b is the bulk density of the powder.

2.2.3. Hausner' ratio

It indicates the flow properties of the powder and is measured and is measured by the ratio of tapped density to the bulk density

H=Dt/Db

Where,

H is the Hausner's ratio, Dt is the tapped density of the powder and Db is the bulk density of the powder.

2.3. Post-Compression parameters: [11-14]

General appearance and organolecptic properties:

The control of a general appearance of a tablet involves the measurement of a number of attributes such as a tablet's size, shape, color, presence or absence of an odor, taste, surface texture,physical flaws and consistency ,and legibility of any identifying markings.

2.3.1. Thickness:

Thickness was determined for 20 pre weighed tablets of each batch using a digital vernier scale and the average thickness was determined in mm. average of three readings were taken and the results were tabulated.

2.3.2. Weight variation:

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated .The tablets meet the USP specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits.

2.3.3. Hardness Test:

Prepared tablets were evaluated for their hardness by using Pfizer hardness tester .scale was adjusted to zero ,load was gradually increased until the tablet fractured.The value of the load at the point gives a measures of hardness of the tablet. Hardness was expressed in kg / cm 2.Triplicate readings were taken and average was computed.

2.3.4. Percentage Friability:

In friability testing the tablets are subjected to abrasion and shock. It gives an indication of the tablets ability to resist chipping and abrasion during transportation and shipping.If the tablet weight is below 650 mg 10 tablets were taken and initial weight was noted .the tablets were rotate in the Roche friabilator for 100 revolutions at 25 rpm. The tablets were dedusted and reweighed for conventional tablets the percentage friability should be less than 1% where as friability values of up to 4% are acceptable for oral disintegrating and chewable tablets.

The percentage friability is expressed as the loss of weight and is calculated by the formula:

$$\textbf{\% Friability} = \frac{\text{(Initial weight of tablets – Final weight of tablets)} \times 100}{\text{Initial weight of tablets}}$$

2.3.5. Content Uniformity:

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Five tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately weighed and the amount of average tablet was taken from the crushed blend. Then the samples were transferred to three 100 ml volumetric flasks and were diluted up to the mark 0.1N HCL solution. The content was shaken periodically and kept for 24 hours for dissolution of the drug completely. The mixtures were filtered and appropriate dilutions were made. The drug content in each tablet was estimated at λ max 290 nm against blank reference and reported.

2.3.6. *In-vitro* dissolution studies

The studies were done on eight station USP dissolution apparatus I (Lab India). 900 ml of the dissolution medium was placed in all the vessels with temperature $37 \pm 0.5^{\circ}$ C. One tablet was placed in each vessel and 10 ml sample was withdrawn from each vessel after specified time intervals and replaced with an equal volume of fresh dissolution medium at the specified time intervals. Filtered the solution through a 0.45 µm filter paper and absorbance

of the standard solution and sample solution was measured in a UV –Visible spectrophotometer at 225 nm using dissolution medium as a blank.

2.3.7. Mathematical modeling for drug release profile

The cumulative amount of Mefenamic acid released from the formulated tablets at different time intervals were fitted in to several kinetic models such as Zero order kinetics, first order kinetics, Higuchi model and Korsemayer-peppas model to characterize mechanism of drug release.

3. Results and Discussion

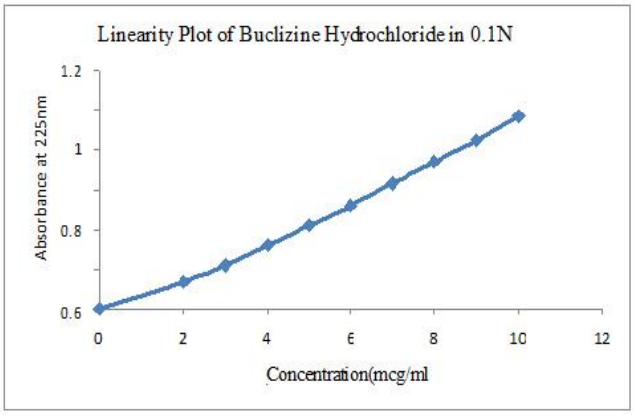


Figure 1: Construction of Calibration Curve

Compatibility Studies:

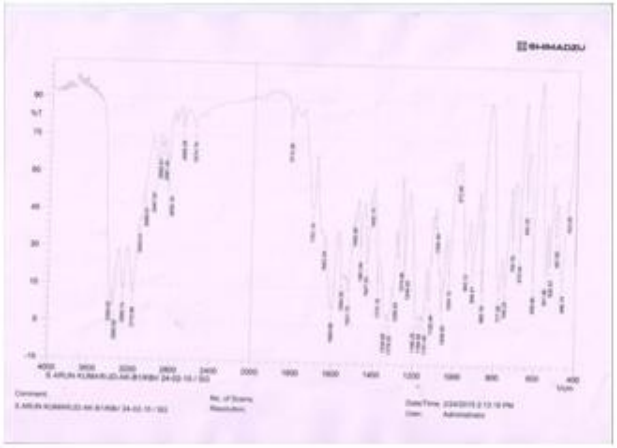


Figure 2: FT-IR Spectrum of Pure Drug (Buclizine hydrochloride) FTIR Spectrum of HPMC

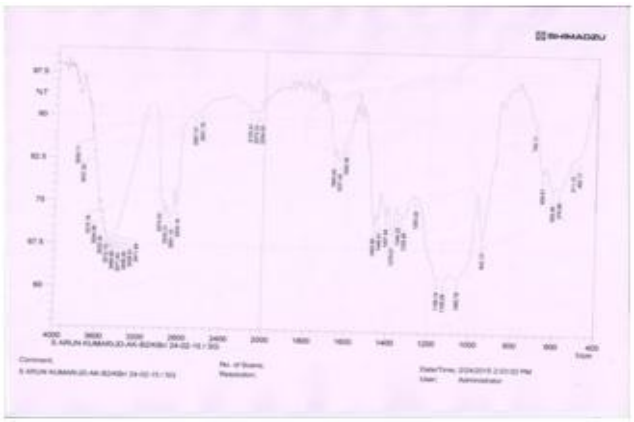


Figure 3: FTIR Spectrum of HPMC

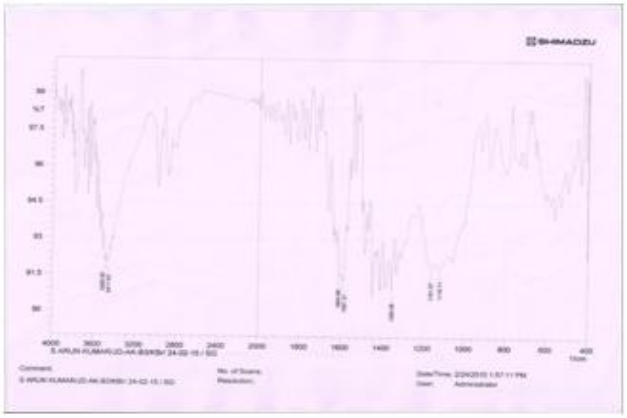


Figure 4: FTIR Spectrum of Ethyl cellulose

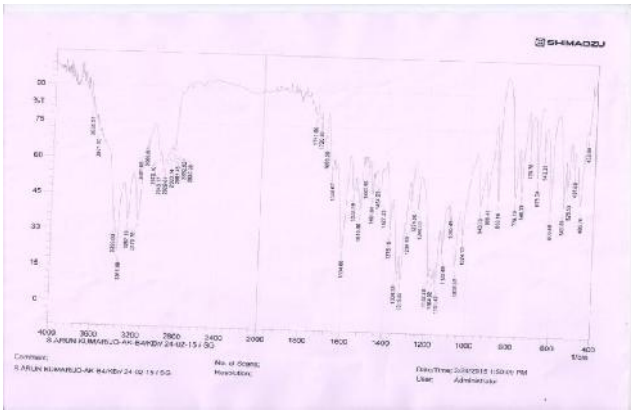


Figure 5: FT-IR Spectrum of Physical mixture of all ingredients

DSC

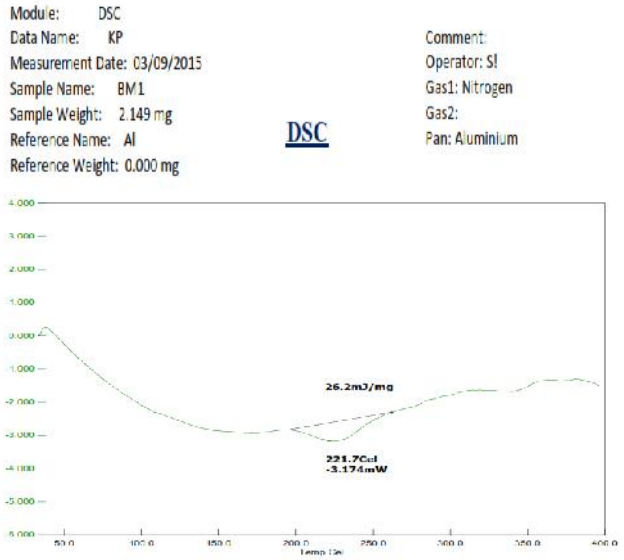
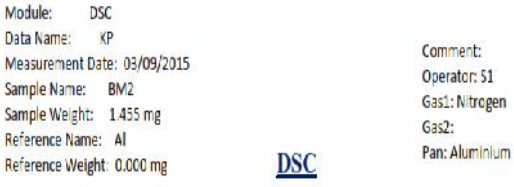


Figure 6: DSC sample-1



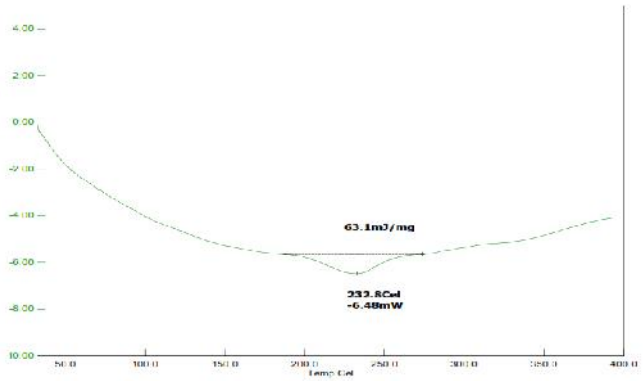


Figure 7: DSC sample-2

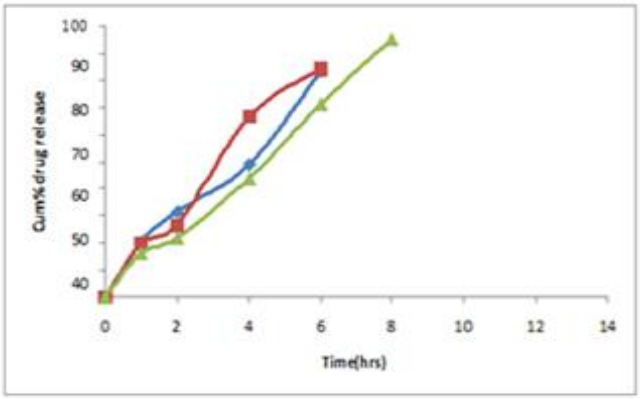


Figure 8: Comparative dissolution profile of batches F1-F3

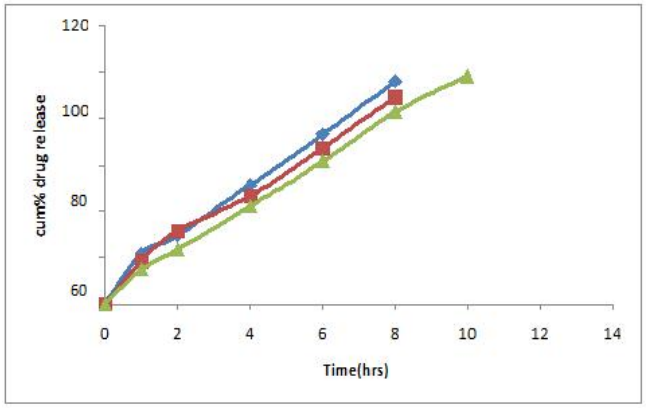


Figure 9: Comparative In vitro drug release F4-F6

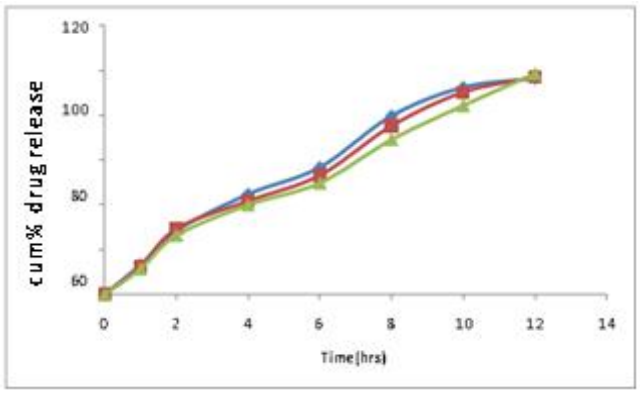
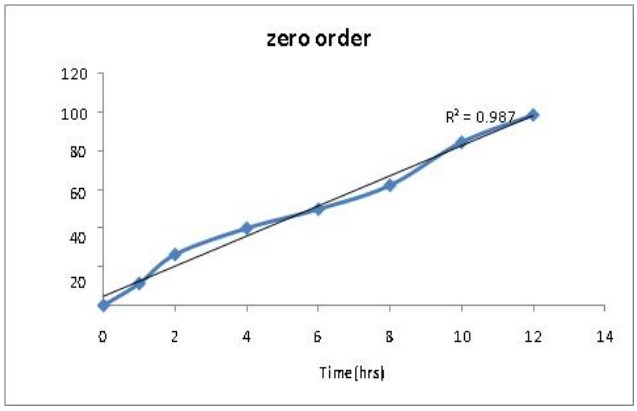
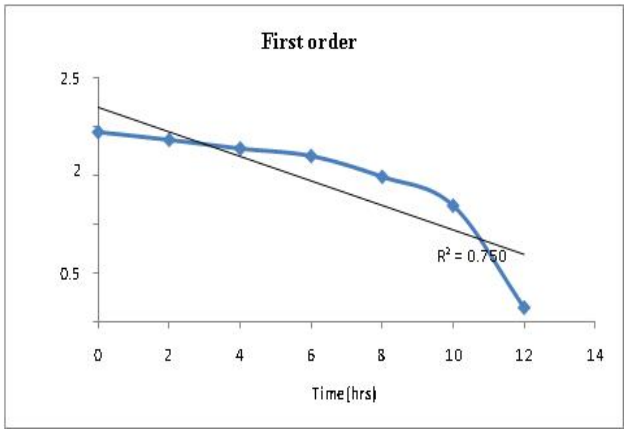
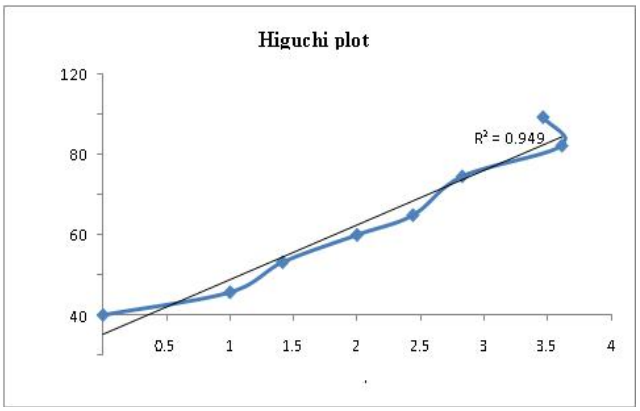


Figure 10: Comparative *In vitro* drug release F7-F9







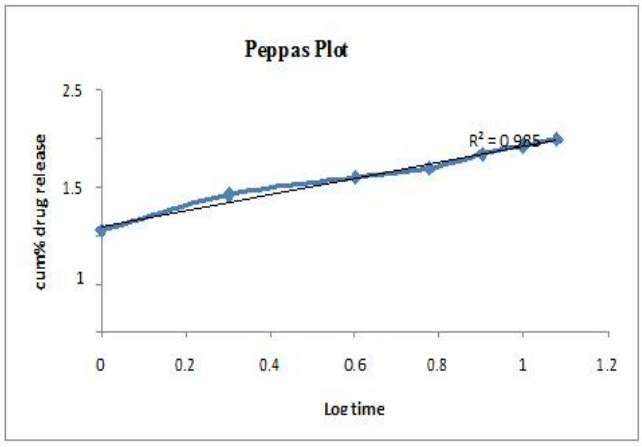


Figure 11: *In-vitro* release kinetics of Buclizine hydrochloride sustained release tablets of F9 formulation.

Table 1: Composition of Buclizine hydrochloride sustained released tablet formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Drug	50	50	50	50	50	50	50	50
Hpmc	12.5	17.5	22.5	-	-	-	22.5	17.5
Ec	-	-	-	25	50	75	25	50
Lactose	377.5	372.5	367.5	365	340	315	342	322
Starch	25	25	25	25	25	25	25	25
Mg.STERATE	10	10	10	10	10	10	10	10
Talc	25	25	25	25	25	25	25	25
Total(Mg)Wt	500	500	500	500	500	500	500	500

Table 2: Standard plot data for Buclizine hydrochloride in 0.1N HCl solution

S.No	Concentration (µg/ml)	Absorbance at 225nm
1	1	0.010
2	2	0.135
3	3	0.219
4	4	0.321
5	5	0.422
6	6	0.530
7	7	0.645
8	8	0.757
9	9	0.862
10	10	0.971

Table 3: Results for Micromeritic properties

Formulation code	Bulk density (mean ± SD) (g /ml)	Tapped density (mean ± SD) (g /ml)	Angle of Repose (mean ± SD)	Carr's index (mean ± SD)	Hausner's ratio (mean ± SD)
F1	0.39±0.16	0.42±0.18	30.16±0.08	7.142	1.0769
F2	0.37±1.26	0.41±018	30.110±0.03	9.756	1.1081
F3	0.41±1.21	0.41±0.16	33.43±0.07	12.765	1.1463
F4	0.38±1.06	0.43±0.29	31.26±0.01	11.627	1.1315
F5	0.39±1.08	0.46±0.26	32.01±0.09	15.217	1.1794
F6	0.42±1.06	0.48±0.39	30.13±0.06	12.536	1.1428
F7	0.39±1.07	0.47±0.08	31.23±0.01	17.021	1.2051
F8	0.41±0.02	0.47±0.19	30.24±0.07	12.765	1.1463
F9	0.41±0.08	0.48±1.26	31.26±0.05	14.583	1.1707

Table 4: Physicochemical Properties of Tablets

S.No	Weight variation(mg)	Thickness (mm)	Hardness Kg/cm2	Friability (%)	Drug content (%)
F1	501.12±0.16	3.12±0.01	4.9±0.30	0.61±0.08	99.9±0.49
F2	500.16±0.04	3.06±0.03	4.5±0.38	0.63±0.01	99.8±0.62
F3	497.23±0.16	3.14±0.08	4.3±0.91	0.68±0.07	99.8±0.99
F4	499.18±0.27	3.06±0.03	3.9±0.43	0.64±0.08	100.1±0.18
F5	498.23±0.18	3.10±0.08	4.1±0.29	0.67±0.03	99.6±0.29
F6	500.19±1.26	3.21±0.01	3.9±0.84	0.71±0.09	99.8±0.39
F7	501.18±0.98	3.20±0.04	3.8±0.49	0.73±0.03	99.7±0.41
F8	498.26±0.17	3.02±0.02	3.7±0.76	0.66±0.04	99.8±0.69
F9	499.26±0.92	3.06±0.01	3.6±0.03	0.65±0.02	100.1±0.26
Limits	500±5%	3.5±0.2mm	NLT5kg /cm2	NMT 1%	100±10%

Table 5: *In-vitro* dissolution data of Buclizine hydrochloride Sustained Release tablets

Cumulative % drug release									
Time (hr)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
1	20.31	19.67	16.26	21.72	18.34	14.98	13.17	12.41	11.34
2	31.27	26.40	21.74	29.46	31.42	23.49	28.39	29.31	26.34
4	63.17	66.72	43.84	51.46	46.42	41.92	44.71	41.72	39.92
6	83.41	84.18	71.34	73.38	67.43	61.82	56.75	53.18	49.76
8	-	-	95	96	89.16	82.92	79.72	75.29	69.12
10	-	-	-	-	-	98.2	92.47	90.31	84.39
12	-	-	-	-	-	-	96.5	97	98.6

6.6: *In-Vitro* Drug Release Kinetics for SR Tablets

Table 6: *In-vitro* drug release kinetics data for formulation F9

Zero order		First order	Higuchi's data		Korsemayer- peppas data	
Time (h)	**Cum.% drug release**	**Time(h) Vs log cum. % of drug remaining**	**SQRT time**	**Cum.% Drug Release**	**Log time**	**Log Cum. %drug release**
1	11.34	1.947	1	11.34	0	1.054
2	26.34	1.867	1.414	26.34	0.301	1.420
4	39.92	1.778	2.00	39.92	0.602	1.601
6	49.76	1.701	2.44	49.76	0.778	1.696
8	69.12	1.489	2.828	69.12	0.903	1.839
10	84.39	1.193	3.612	84.39	1	1.926
12	98.6	0.146	3.464	98.6	1.079	1.993

Discussion

DSC:

DSC spectra of the pure drug has endothermic peak with 221.7 Cel and 3.174 mw. The mixture sample contain drug (Buclizine hydrochloride), Ethyl cellulose, HPMC the endothermic peak is 232.8 Cel and -6.48 Mw.

Micromeretics

The flow properties and other derived properties evaluated for all the 9 formulations were proved to be within limits showing good flow properties.

Physico-chemical properties

The prepared 9 Sustained release tablets formulations were evaluated for physic chemical parameters and were proved to be within limits (As per USP).

***In-vitro* drug release studies**

The *in-vitro* drug release studies were conducted using Purified water as dissolution medium and the results were tabulated and also represented graphically by taking Time (hrs)on X-axis and cumulative percentage drug release on Y-axis. In formulation F1 the Buclizine hydrochloride Sustained Release tablet were prepared with 50mg of drug and12.5mg of HPMC 15CPA and Lactose 377.5mg, they shown drug release of -%in water at end of 12^{th} hour. In formulation F2 the Buclizine hydrochloride Sustained release tablet were prepared with 50mg of drug and 17.5mg of HPMC 15CPA and Lactose 372.5mg they shown drug release of - % in water at end of 12^{th} hour. In formulation F3 the Buclizine hydrochloride Sustained release tablet were prepared with 50mg of drug and 22.5mg of HPMC 15CPA and Lactose 367.5mg they shown drug release of -% in water at end of 112^{th} hour. In formulation F4 the Buclizine hydrochloride Sustained Release tablet were prepared with 50mg of drug and 25mg of Ethyl cellulose, Lactose 365mg they shown drug release of-% in water at end of 12^{th} hour. In the formulation F5 the Buclizine hydrochloride Sustained Release tablet were prepared with 50mg of drug and 50mg of Ethytl cellulose, Lactose 340mg they shown drug release of -% in water at end of 12^{th} hour. In the formulation F6 the Buclizine hydrochloride Sustained Release tablet were prepared with 50mg of drug and Ethyl cellulose 75mg and Lactose 315mg they shown drug release of-% in water at end of 12^{th} hour. In the formulation F7 the Buclizine hydrochloride Sustained Release tablet were prepared with 50mg of drug and22.5mg HPMC15CPA, Ethyl cellulose 25mg, Lactose 342.5mg they shown drug release of 96.5% in water at end of 12^{th} hour. In the formulation F8 the Buclizine hydrochloride Sustained Release tablet were prepared with 50mg of drug and HPMC 17.5mg, Ethyl cellulose 50mg, Lactose 322.5mg they shown drug release of 97% in water at end of 12^{th} hour. In formulation F9 the Buclizine hydrochlorides Sustained Release tablet was prepared with 50mg of drug and HPMC 15CPA 12.5mg, Ethyl cellulose 7.5mg, Lactose 302.5mg they shown drug release of 98.6% in water at end of 12^{th} hour. Among all the 9 formulations (F1-F9) the F9 formulation shows better drug release. The mechanism of this formulation follows zero order and non-fickian diffusion transport type.

4. Conclusion

Buclizine hydrochloride sustained release tablets were prepared by using HPMC as polymer to retard release and achieve required dissolution profile. It was concluded that, percent drug release was increased with decrease in the concentrations of HPMC. 12 hour drug release profile may improve patient compliance and better therapeutic effect in treatment of allergy. Hence, the optimized formulations seems to be stable.

5. References

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