IJPSR (2014), Vol. 5, Issue 4 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 03 November, 2013; received in revised form, 03 January, 2014; accepted, 16 March, 2014; published 01 April, 2014

FORMULATION AND EVALUATION OF GASTRORETENTIVE DELIVERY OF TIZANIDINE HYDROCHLORIDE USING NATURAL POLYMERS

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Keywords:

Tizanidine hydrochloride, HMPC, invitro drug release, buoyancy

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ABSTRACT: The present investigation concerns the design and evaluation of floating tablets of Tizanidine hydrochloride, which after oral administration are designed to prolong the gastric residence time and increased drug bioavailability. It is a centrally acting α2 adrenergic agonist. It is used in the treatment of migraine headaches, spasms and anticonvulsant. The dosage was designed by using natural polymers, Guar gum, Xanthan gum, Karaya gum, Psyllium and HPMC. Floating tablets prepared by direct compression technique. The prepared floating tablets were evaluated in terms of their precompression parameters, friability, hardness, uniformity of weight, drug content, swelling index, *in-vitro* dissolution studies. The floating properties and drug release studies were determined using 0.1N HCl as a dissolution medium. The best formulation was determined based on the buoyancy and drug release parameters.

INTRODUCTION: Tremendous advances have been seen in oral controlled drug delivery systems in the last two decades. In the development of oral controlled drug delivery system, one of the main challenges is to modify the GI transit time. Gastric emptying of pharmaceuticals is highly variable and is dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence times usually range between 5 minutes and 2 hours. Drugs having a short half-life are eliminated quickly from the blood circulation. Various oral controlled delivery systems like gastro retention dosage forms have been designed to overcome this problem and release the drug to maintain its plasma concentration for a longer period of time.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(4).1533-38

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(4).1533-38

Tizanidine hydrochloride has low bioavailability of 3.5-4hrs. It needs daily dosage of 2mg for three times. In order to increase the bioavailability and decrease the dosing, we need to formulate it in the form of sustained drug delivery.

In all sustained deliveries, Gastroretentive drug delivery plays an important role. The present study focus on the development of floating tablets of Tizanidine hydrochloride using different polymer grades to achieve a sustained release for long time.

MATERIALS AND METHODS: Tizanidine hydrochloride, Guar gum, Karaya gum, Xanthan gum, Psyllium are obtained from Sipra Labs limited, Hyderabad

Methods: Different formulations were prepared by direct compression technique. All the ingredients were passed through the sieve and placed in a polybag and mixed thoroughly. Magnesium stearate and talc were added later, and citric acid was added before tablet punching. The composition of all the formulations was shown in the **Table 1**.

TABLE 1: COMPOSITION OF DIFFERENT FORMULATIONS OF TIZANIDINE HCL

S. No.	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
Tizanidine hydrochloride	10	10	10	10	10	10	10	10	10	10	10	10
HPMC K4M					10	20		10	20			
Guar gum	60	80	100									
Xanthan gum				60	80	100						
Karaya gum							60	80	100			
Psyllium										60	80	100
Calcium carbonate	40	40	40	40	40	40	40	40	40	40	40	40
Citric acid	10	10	10	10	10	10	10	10	10	10	10	10
MCC	73	53	33	73	43	23	73	43	23	73	63	33
Magnesium stearate	4	4	4	4	4	4	4	4	4	4	4	4
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Total	200	200	200	200	200	200	200	200	200	200	200	200

Evaluation Studies:

1. **Precompression Studies:**

a. **Bulk Density (gm / ml):** Apparent Bulk density (gm/ml) was determined by pouring gently about 5 gm of drug and excipients sample through a glass funnel into a 50 ml graduated measuring cylinder. Then after pouring the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. the volume measured was called as the bulk volume and the bulk density was calculated by following formula

Bulk density = Wight of the powder / Bulk volume

b. **Tapped Density (gm / ml):** Tapped density was determined by pouring gently about 5 gm of drug and excipients sample through a glass funnel into a 50 ml graduated measuring cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. Volume occupied by the sample after tapping were recorded and tapped density was calculated by using following formula.

Tapped density = Weight of powder / Tapped volume

c. **Carr's Compressibility Index (%):** Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density.

Carr's index = (Tapped density – Bulk density / Tapped density) × 100

d. **Hausner's Ratio:** Hausner's ratio provides an indication of the degree of the densification which could result from vibration of the feed hopper. A lower value indicates better flow and vice versa.

Hausner's Ratio = Tapped density / Bulk density

e. **Angle of Repose:** Angle of repose is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The flow characteristics of powder mixture were studied by measuring the angle of repose employing fixed funnel method.

Angle of repose (θ) = $\tan^{-1}$ (h / r)

The Precompression or Micromeretic parameters of all formulations were shown in the **Table 2**.

2. **Post compression parameters:**

a. **Weight Variation:** Formulated tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated by the following formula

% Weight variation = [(Average weight – Individual weight) / Average wt] × 100

The weight variation of all the formulations were shown in **Table 3** [8].

b. **Hardness:** Hardness of the tablets was determined by using Monsanto hardness tester.

The tablet to be tested is held in fixed and moving jaw and reading of the indicator adjusted to zero. Then force to the edge of the tablets was gradually increased by moving the screw knob forward until the tablet breaks. The reading was noted from the scale which indicates the pressure required in kg to break the tablet. The hardness of the tablets depends on the weight of the materials used, apace between the upper and lower punches at the time of compression and pressure applied during compression. The Hardness test of all the formulations were shown in **Table 3** [9].

c. **Friability:** The Roche friability test apparatus was used to determine the friability of the tablets. Randomly selected twenty pre-weighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The acceptable limits of the weight loss should not be more than 0.8%. The Friability of all the formulations was shown in **Table 3**. The percentage friability was calculated according to the following formula;

% Friability = [(Initial weight – Final weight) / Initial weight] × 100

d. Floating lag time and Total floating time: Floating characteristics of the prepared formulations were determined using the 0.1N HCL. The tablets were placed in a 100ml beaker containing 0.1 N HCl at 37 ± 0.5^0 C. The time required for the tablet to rise to the surface and float on solution (Floating lag time) and the time during which dosage form remain buoyant on the solution (Total floating time) were measured [6]. The Floating lag time and total floating time of all the formulations were shown in **Table 4**.

e. **Drug Content uniformity:** Over ten tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately average weighed amount of tablets triturate was taken for analysis. The powder material was transferred in to a 100ml volumetric flask and it was diluted with the 0.1 N HCl. The content was shaken well and kept for 30 minutes for dissolving the drug. Then it was filtered and 1 ml of the filtrate was diluted to 10 ml using 0.1 N HCl to obtain 10 µg/ml solution then the absorbance was measured at 319nm [5]. The Drug content uniformity of all the formulations was shown in **Table 3**.

f. ***In-vitro* Dissolution studies:** *In vitro* drug release study of the samples was carried out by using USP – type II dissolution apparatus (Paddle type). The 0.1 N HCL was used as the dissolution medium. The 900ml of 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37 ± 0.5^oC and rpm of 50. 5 ml of sample was withdrawn after 0.5, 1, 2, 4, 6, 8, 10, and 12 hours and the same was replaced with fresh dissolution medium (37^oC).

Collected samples were analyzed at 319nm using 0.1 N HCL as blank [6]. The drug release experiments were conducted in triplicate. The *in vitro* drug release study was shown in **Table 5** and *in vitro* drug release graph, Cumulative % drug released vs time for the formulations T1-T3 was shown in the **Fig. 1** and T4-T6 was shown in the **Fig. 2**, T7-T9 was shown in the **Fig. 3** and T10-T12 was shown in the **Fig. 4** [12].

RESULTS AND DISCUSSIONS:

1. Precompression Evaluations:

TABLE 2: MICROMERETIC PROPERTIES OF FORMULATIONS T1-T12

Formulation	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose
T1	0.499 ±0.002	0.527±0.005	5.56 ±0.018	1.15 ±0.002	23.15 ±0.571
T2	0.456 ±0.007	0.531 ±0.008	7.89 ±0.021	1.06 ±0.001	22.67 ±0.448
T3	0.461 ±0.002	0.487 ±0.008	8.51 ±0.036	1.08 ±0.000	24.87 ±0.633
T4	0.485 ±0.001	0.522 ±0.009	7.56 ±0.045	1.13 ±0.002	29.79 ±0.522
T5	0.478 ±0.002	0.469 ±0.003	6.77 ±0.044	1.09 ±0.001	24.83 ±0.271
T6	0.505 ±0.003	0.495 ±0.003	8.96 ±0.025	1.10 ±0.002	23.19 ±0.444
T7	0.463 ±0.002	0.477 ±0.002	9.73 ±0.012	1.07 ±0.001	22.73 ±0.562
T8	0.472 ±0.003	0.515 ±0.004	7.56 ±0.081	1.10 ±0.000	27.85 ±0.456
T9	0.489 ±0.002	0.453 ±0.006	5.59 ±0.051	1.09 ±0.002	24.82 ±0.554
T10	0.502 ±0.001	0.483 ±0.007	6.99 ±0.058	1.04 ±0.000	25.34 ±0.436
T11	0.488 ±0.002	0.461 ±0.005	7.39 ±0.085	1.07 ±0.000	24.11 ±0.542

T12	0.492 ±0.003	0.514 ±0.006	8.55 ±0.067	1.12 ±0.002	33.77 ±0.473

2. Post Compression Evaluation:

TABLE 3: PHYSICAL PROPERTIES OF FORMULATIONS T1-T12

S. No.	Weight Variation (mg)	Hardness (kg/ cm^2)	Friability (%)	Drug Content (%)
T1	199	3.8	0.58	99.08
T2	201	4.0	0.66	100.02
T3	198	4.5	0.75	98.36
T4	200	4.2	0.85	99.71
T5	199	4.3	0.53	100.02
T6	198	3.9	0.68	101.03
T7	200	4.0	0.79	99.73
T8	199	4.4	0.72	99.87
T9	200	3.9	0.59	99.89
T10	198	4.0	0.62	99.99
T11	198	4.2	0.72	100.07
T12	199	3.7	0.73	101.56

In-vitro Buoyancy:

TABLE 4: FLOATING LAG TIME AND TOTAL FLOATING TIME OF DESIGNED FORMULATIONS

S. No.	Floating Lag Time (sec)	Total Floating Time (hrs)
T1	030	>12
T2	029	>12
T3	025	>12
T4	040	>12
T5	026	>13
T6	020	>13
T7	030	>14
T8	029	>15
T9	025	>15
T10	026	>12
T11	028	>12
T12	029	>12

In vitro Drug Release Study:

TABLE 5: DRUG RELEASE KINETIC DATA OF TIZANIDINE HYDROCHLORIDE WITH GUAR GUM, XANTHAN GUM, KARAYA GUM, PSYLLIUM

Formulation	Correlation coefficient				
	Zero order	First order	Higuchi	Peppas	Hixon Crowell
T1	0.711	0.971	0.929	0.390	0.917
T2	0.765	0.827	0.946	0.410	0.980
T3	0.759	0.923	0.968	0.448	0.943
T4	0.833	0.944	0.979	0.662	0.991
T5	0.989	0.956	0.987	0.639	0.986
T6	0.991	0.969	0.974	0.687	0.990
T7	0.962	0.988	0.995	0.627	0.992
T8	0.992	0.977	0.998	0.614	0.990
T9	0.991	0.987	0.996	0.616	0.991
T10	0.789	0.933	0.997	0.702	0.990
T11	0.885	0.953	0.995	0.626	0.991
T12	0.887	0.977	0.998	0.636	0.992

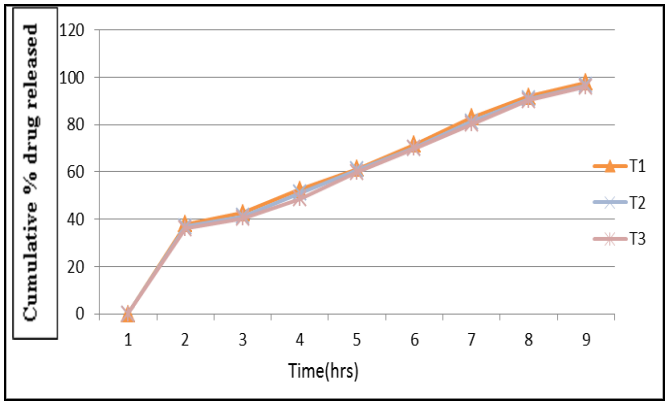

FIG. 1: *IN VITRO* DISSOLUTION PROFILE OF FORMULATION F1-F3

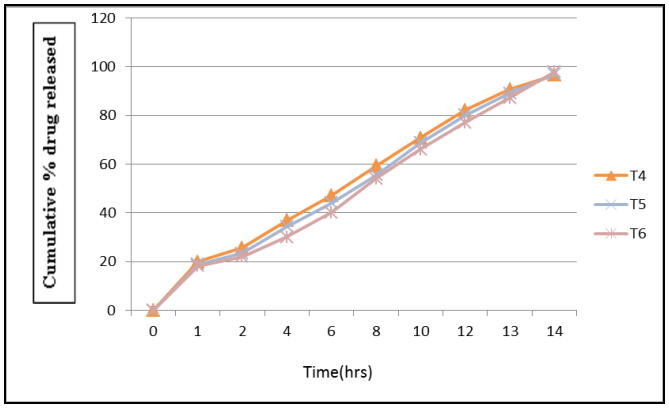

FIG. 2: *IN VITRO* DISSOLUTION PROFILE OF FORMULATION T4-T6

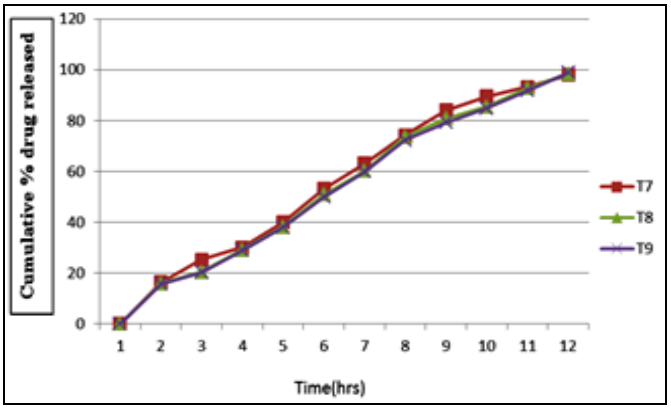

FIG. 3: *IN VITRO* DISSOLUTION PROFILE OF FORMULATION T7-T9

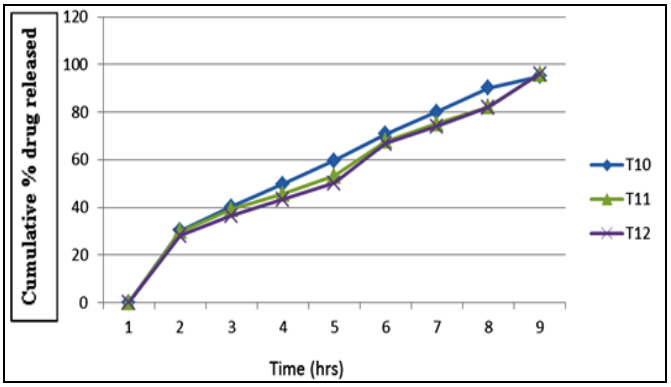

FIG. 4: *IN VITRO* DISSOLUTION PROFILE OF FORMULATION T10-T12

CONCLUSION: From the above studies, it was concluded that all the formulations designed with gas generating agents showed sustained release or zero order drug release. The formulations designed with natural polymer and small amounts of HPMC in case of Xanthan gum and Karaya gum showed better drug release than their the formulations without HPMC. From this study it was concluded that Tizanidine hydrochloride formulated with Karaya gum with HPMC showed gastric retention up to 16hrs. T9 is the best formulation among all designed formulations. The best formulated was concluded based on drug release and Total floating time**.**

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How to cite this article:
Boorlagadda H, Sandeep V, Reddy AM and Babu PS: Formulation and evaluation of Gastroretentive Delivery of Tizanidine hydrochloride using natural polymers. *Int J Pharm Sci Res* 2014; 5(4): 1533-38.doi: 10.13040/IJPSR.0975-8232.5(4).1533-38