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DESIGN, FORMULATION AND *IN VITRO* EVALUATION OF SUSTAINED RELEASE PULSATILE CAPSULE OF METOPROLOL TARTRATE

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ABSTRACT: Pulsatile system is gaining a lot of interest as it increases patient compliance by means of providing time and site specific drug delivery system. This work will aim at the design of a sustained release formulation with potential use of metoprolol tartrate capsule which is used in the treatment of hypertension. The design involves the preparation of cross linked hard gelatin capsules by using formaldehyde, then the drug diluents mixture loaded in, which was separated by using hydrogel plugs of different polymers, such as, HPMC 15cps, HPMC 50cps, HPMC 100cps, HPMC K4M, HPMC K15M, HPMC K100M, xanthan gum, carbomer 940, carbopol 971, sodium CMC and sodium alginate of two different amounts (75mg and 100mg respectively). Prepared formulations were subjected to evaluation of various phycal parameters and in vitro drug release studies. From the in vitro dissolution studies it was found that by increasing the amount of polymer, release rate was decreased. 75mg of HPMC 15cps showed 91.23% drug release in 5hr whereas 100mg showed 96.68% drug release in 7hr. Similar decrease in the release rates were found with the increase of other polymers of the study. Furthermore the release data was fitted to various mathematical models such as Zero order, First order, Higuchi, Korsmeyer Peppas and Hixson-Crowell kinetics. The drug release follows mixed order kinetics and mechanism was found to be non-Fickian diffusion. As this drug delivery system is still in the developmental stage much more research can be performed to make it as a practical clinical alternative.

INTRODUCTION: The oral route of drug delivery is always considered as the most convenient means of drug administration. It has the greatest degree of patient compliance, as a result providing reproducible and effective plasma concentrations *in vivo* [1]. For sustained release systems, the oral route of administration has received the most attention with respect to research over various issues. This is due to that there is more flexibility in dosage regimen for the oral routes than any other routes.

The reason that the oral route achieved such popularity is due to its ease of administration and traditional belief that by oral administration the drug is well absorbed [2]. Traditionally, drug delivery systems have focused on a prolonged drug output with the objective of minimizing peaks and valleys of drug concentrations in the body to optimize drug efficacy and to reduce adverse effects.

A reduced dosing frequency and improved patient compliance can also be expected for the prolonged release drug delivery systems, compared to immediate release preparation [3]. There are certain conditions for which such a sustained release pattern is not suitable at all. This type of conditions demands release of drug after a lag time. In other words the drug does not require to be released right after administration, instead it starts releasing after

a suitable lag time. Such a release pattern is known as pulsatile release. Recent studies have revealed that diseases have a predictable cyclic rhythm that the timing of medication regimens can improve the outcome of a desired effect. This condition demands release of drug as a pulse after a time lag and such system has to be designed in a way that complete and rapid drug release should follow the lag time. Such systems are known as pulsatile drug delivery systems (PDDS) [4].

PDDS delivers drug in rapid and burst manner within a short time period immediately after a programmable lag phase [5]. There are many situations where drug is needed to be released immediately (after bursting the delaying film a coat) at specific site. These situations, therefore, compel designing a delayed fast release systems. These systems are mainly appropriate for drugs that are metabolized to pharmacological active compounds, drugs which have long *in vivo* half lives showing an inherently prolonged duration of action, drugs with very short in vivo half lives which require a prohibitively large amount of active ingredients in dosage form, drugs which are required in large doses for therapeutic effect and drugs which are required in very low dose. Additionally a delayed burst release can also be utilized for enhancing absorption, reducing side effects, increasing and decreasing dose [6].

Cardiovascular diseases, several functions (e.g. BP, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day whereas platelet aggregation is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. Careful analysis of trials illustrates that myocardial infarction (MI), stroke, ventricular ectopy, and sudden cardiac death occur between 6am and noon.

The peak blood pressure is between 6am and noon, with activation of the sympathetic nervous system prior to awakening, blood pressure begins to increase with the heart rate. These changes in blood pressure corresponds the morning activation in catecholamines, renin, and angiotensin. Commonly used drugs are- nitroglycerin, beta blockers, calcium channel blockers, ACE inhibitors etc. Metoprolol tartrate is a selective beta1-adrenoreceptor blocking agent. It also inhibits beta2-adrenoreceptors, chiefly located in the bronchial and vascular musculature. The mechanism of the antihypertensive effects of beta-blockers has not been fully elucidated.

Pulsatile drug delivery system is likely to be successful for diseases such as asthma, peptic ulcer, cardiovascular diseases, arthritis, hypertension, and hypercholesterolemia. Hence, metoprolol tartrate was used as the prototype drug. Based on this concept and a difference in the pH throughout the GIT, a time & pH dependent pulsatile drug delivery system was designed which will leave the stomach, arrive at the ileocaecal junction in 4-6 hours after administration.

MATERIALS AND METHODS:

- **Materials:** Metoprolol tartrate was obtained as a gift sample from Popular Pharmaceuticals Ltd. HPMC of different grades, xanthan gum, carbomer 940, carbopol 971, sodium-cmc and sodium-alginate were from Loba Chemicals, India. The empty capsule shells of size "0" were gifted by Eskayef Bangladesh Limited.

- **Formaldehyde treated crossed linked gelatin capsule:**
  A total of 25 hard gelatin capsule shells of size "0" were taken and their body were separated from the cap and then placed over a wire mesh. 25ml of 37% v/v of formaldehyde solution was taken in an empty dessicator. 2.5g of potassium permanganate was added into the formaldehyde. The wire mesh was kept inside the dessicator and it was closed and sealed.

  The capsule body reacted with the formaldehyde vapor for 4 hours. After that they were removed and kept on a filter paper and dried in open atmosphere for the next 48 hours to aid the removal of the formaldehyde residues. The capsule bodies were kept in an airtight container for further use [7].

- **Formulation of the Pulsatile capsules:** 50 mg of metoprolol tartrate and 100 mg lactose were

accurately weighed and taken in a mortar. Metorolol tartrate and lactose were then evenly blended for about 15 minutes. The blended mixture was stored in a polyethene bag for

further use. Different formulations were prepared using the polymers as hydrogel plugs. The formulations are given in **Table 1**.

TABLE 1: ILLUSTRATING DIFFERENT FORMULATION COMPOSITION

Formulation code	Polymer	Grades	Drug lactose mixture	Amount of polymer used plug
F-1	HPMC	15cps	150mg	75mg
F-2	HPMC	50 cps	150mg	75mg
F-3	HPMC	100cps	150mg	75mg
F-4	HPMC	K4M	150mg	75mg
F-5	HPMC	K15M	150mg	75mg
F-6	HPMC	K100M	150mg	75mg
F-7	Xanthan Gum	Nil	150mg	75mg
F-8	Carbomer	940	150mg	75mg
F-9	Carbopol	971	150mg	75mg
F-10	Sodium-CMC	Nil	150mg	75mg
F-11	Sodium-Alginate	Nil	150mg	75mg
F-12	HPMC	15cps	150mg	100mg
F-13	HPMC	50 cps	150mg	100mg
F-14	HPMC	100cps	150mg	100mg
F-15	HPMC	K4M	150mg	100mg
F-16	HPMC	K15M	150mg	100mg
F-17	HPMC	K100M	150mg	100mg
F-18	Xanthan gum	Nil	150mg	100mg
F-19	Carbomer	940	150mg	100mg
F-20	Carbopol	971	150mg	100mg
F-21	Sodium-CMC	Nil	150mg	100mg
F-22	Sodium-Alginate	Nil	150mg	100mg

- **Filling of capsules:**
Hard gelatin capsules of size '0' were taken. Treated body and untreated caps were used for filling purpose. Six capsules for each formulation were prepared manually by the following procedure:

The cap and body of the capsule was removed manually by hand. The drug lactose mixture (50mg) that was equivalent to 25mg dose of metoprolol tartrate was filled into the empty capsule body forming the second dose of the medication. The bodies containing drug lactose mixture were then plugged with different amounts of polymers mentioned in the table just above the second dose and lightly pressed with a glass plunger. In the same manner the first dose of same quantity followed by polymer layer was then filled in the same capsule body above the previous layers. After that equivalent amount of drug lactose mixture were weighed and placed over the first dose

acting as the immediate release (dose) of the drug. Then the cap was joined with the body and stored into an air tight container for further use.

- **Evaluation of formaldehyde treated capsules:**
Different type of tests both physical and chemical was carried out for treated and untreated capsules. Properties like shape, stickiness, color, odor etc were checked visually. Length, Diameter (both external and internal) and thickness was measured with the help of a Vernier caliper [8].

- **Qualitative test for free formaldehyde:**
A suitable volume of formaldehyde solution was diluted with water to give a solution containing 20µg/ml formaldehyde. Twenty five formaldehyde treated bodies were cut into small pieces and taken into a beaker containing 40ml of distilled water. This was stirred for 1hr

with a magnetic stirrer to solubilize the free formaldehyde. The solution was filtered into a 50ml volumetric flask, washed with distilled water and volume was made up to 50ml with washings.

To 1ml sample solution in a test tube, 4ml of water and 5ml of acetyl acetone solution were added; the test tube was placed in a water bath at 40°C for 40min. At the same time reference solution was placed in the same manner using 1ml of standard formaldehyde solution. The sample solution was not more intensely colored than the standard solution inferring that less than 20µg/ml of free formaldehyde was present in 25 capsule bodies [8].

- **Evaluation of modified pulsincap:**
  Dissolution studies were carried out by using USP XXIII dissolution test apparatus by rotating basket method in different media. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2 and 6.8 were sequentially used referred to as sequential pH change method. During the experiment the pH 1.2 medium was first used for 2 hours (since the average gastric emptying time is 2 hrs) and then the media was removed and a new media of pH 6.8 was added and the procedure continued for the next 10 hours. The amount of media in each time was 900ml. To avoid floating the capsules were placed within baskets. The procedure was maintained at 37±0.5° C and the rotation speed of the basket was 50rpm. Ten milliliters of sample were withdrawn from the dissolution media at predetermined intervals. Same amount of fresh buffer was replaced during each withdrawal. The absorbance was measured at 275nm by UV absorption spectroscopy.

Data obtained was subjected to kinetic treatment to understand release mechanism. Several mechanisms of drug release such as Zero order, First order, Higuchi, Korsmeyer Peppas and Hixon-Crowell were studied to ascertain the kinetic modelling of drug release.

RESULTS AND DISCUSSION: The capsular filling of pulsatile drug delivery system of metoprolol tartrate for the treatment of hypertension was done manually. Various polymers were used in this process. According to the physical parameters in **Table 2** the length of the body of the capsule was found to be 17.9 and 18.3 mm for untreated and treated capsules respectively. The external diameter was found to be 6.9 and 7.1 mm for untreated and treated capsules. The thickness of the capsule was found to be in the range of 0.3-0.4 mm.

The formaldehyde treated capsules were found to be slightly thicker; as a result they displayed much better sustained release activity compared to an untreated capsule. The increase of thickness was possibly due to the treatment process. Average weight of empty capsules was found in the range of 92.4-94.1 mg. Treatment did not influence the average capsule weight significantly. During the dissolution of untreated capsule it was seen that the body and cap dissolved between 15 minutes. On the other hand during the dissolution of treated capsule it was been seen that the cap dissolved within 15 minutes but the treated body remained intact. Drug and polymer did not have any chemical or physical interaction was proved by FTIR studies. Amount of metoprolol tartrate in each capsule was 75mg that was divided into three equal dose separated by polymer layers.

TABLE 2: PHYSICAL CHARACTERISTICS OF EMPTY GELATIN CAPSULES WITH OR WITHOUT TREATMENT

Type of capsules	Length (mm)		External diameter (mm)		Thickness (mm)		Weight of empty capsule (mg)
	Cap	Body	Cap	Body	Cap	Body	
Untreated	10.9±0.1	17.9±0.3	7.4±0.2	6.9±0.1	0.2±0.1	0.2±0.0	93.8±2.2
Formalin Treated	-	18.3±0.1	-	7.1±0.1	-	0.2±0.0	94.9±2.1

From the zero order release kinetics of formulations containing 75 mg polymer layer, it was seen that the highest release was for F2 (99.69%) in 8 hours respectively (**Fig. 1**). F3, F7

and F9 gave their highest release at around 11 hours. The other formulations gave their highest release in the range of 8-10 hours of administration. On the other hand for the formulations containing 100 mg of polymer layer displayed highest result (99.23%) for F13 in 8 hours. F18, F19 and F20 gave their highest release at 11 hours. In the meanwhile the time required for other formulations to give their highest release ranged from 7-10 hours. It was seen that a negative correlation existed between the increasing amount of polymer and the percent drug release.
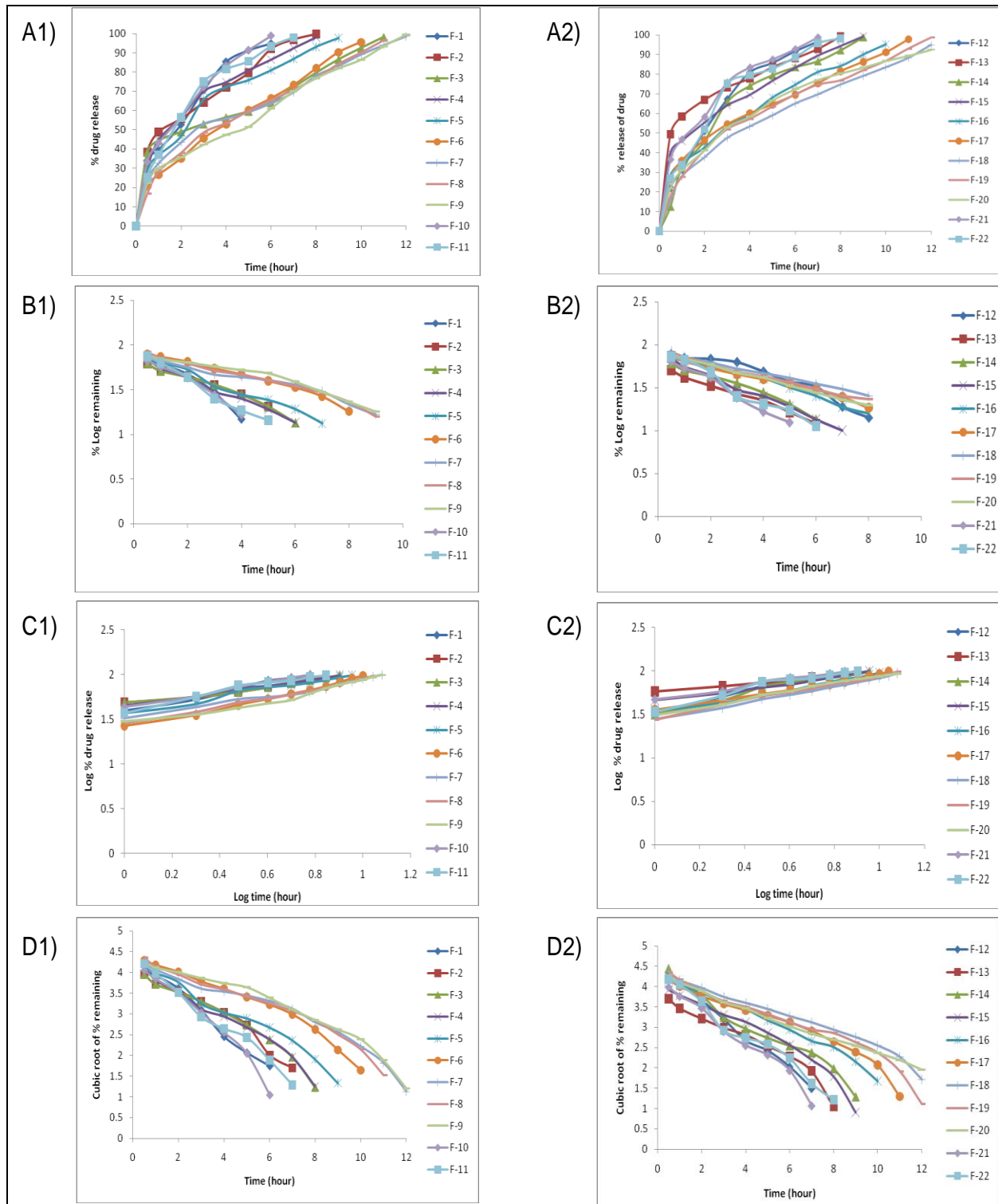

FIG.1: ZERO ORDER RELEASE KINETICS (A), FIRST ORDER RELEASE KINETICS (B), KORSMEYER RELEASE KINETICS (C) AND HIXSON-CROWELL RELEASE KINETICS (D) OF FORMULATION F1-F11 AND F2-F22 CONTAINING DIFFERENT POLYMER GRADES USED IN THE STUDY WITH AN AMOUNT OF 75mg (1) AND 100MG (2) RESPECTIVELY

TABLE 3: INTERPRETATION OF RELEASE RATE CONSTANTS AND R^2 VALUES FOR DIFFERENT RELEASE KINETICS

Formulations	Zero Order		First Order		Higuchi		Korsmeyer		Hixson Crowell	
	R^2	K_0	R^2	K_1	R^2	K_H	R^2	n	R^2	K_H
F-1	0.905	14.47	0.945	-0.182	0.847	244.2	0.983	1.590	0.988	0.446
F-2	0.866	10.27	0.987	-0.101	0.946	235.3	0.955	1.660	0.962	0.336
F-3	0.873	6.589	0.893	-0.067	0.958	227.5	0.975	1.663	0.973	0.325
F-4	0.857	10.2	0.941	-0.089	0.924	234.2	0.995	1.649	0.975	0.339
F-5	0.884	9.207	0.955	-0.066	0.911	227.5	0.980	1.566	0.977	0.303
F-6	0.966	8.490	0.979	-0.078	0.866	213.4	0.991	1.395	0.958	0.257
F-7	0.926	6.806	0.960	-0.069	0.920	209.8	0.979	1.498	0.937	0.231
F-8	0.948	7.624	0.976	-0.075	0.888	211.5	0.994	1.459	0.958	0.233
F-9	0.963	7.150	0.950	-0.070	0.886	212.1	0.994	1.459	0.938	0.235
F-10	0.905	14.51	0.983	-0.169	0.867	249.1	0.995	1.628	0.970	0.514
F-11	0.884	12.77	0.987	-0.166	0.851	249.2	0.972	1.595	0.980	0.428
F-12	0.907	12.88	0.907	-0.065	0.814	246.9	0.978	1.521	0.996	0.423
F-13	0.746	8.994	0.992	-0.107	0.994	225.4	0.982	1.754	0.941	0.303
F-14	0.880	10.10	0.977	-0.084	0.838	239.1	0.970	1.533	0.973	0.325
F-15	0.851	8.60	0.886	-0.069	0.966	223	0.988	1.644	0.946	0.314
F-16	0.917	8.032	0.915	-0.056	0.923	213.9	0.990	1.517	0.986	0.245
F-17	0.906	7.162	0.979	-0.078	0.866	213.4	0.990	1.542	0.948	0.232
F-18	0.932	6.794	0.995	-0.066	0.900	206.5	0.998	1.438	0.976	0.199
F-19	0.920	7.01	0.994	-0.073	0.902	214.9	0.994	1.459	0.945	0.232
F-20	0.886	6.619	0.998	-0.079	0.924	209.1	0.994	1.459	0.993	0.193
F-21	0.846	11.84	0.990	-0.163	0.918	245.5	0.983	1.669	0.978	0.415
F-22	0.870	11.08	0.975	-0.150	0.865	244.5	0.953	1.565	0.981	0.384

It was observed from **Table 3** that most of the formulations followed Korsmeyer Peppas equation and few formulations followed first order release kinetics. The *in vitro* data was also subjected to Hixon Crowell and Higuchi model. The 'n' values from the Korsmeyer Peppas plots concluded that all the formulations followed Super case II transport. Case II generally refers to erosion of polymeric chain and anomalous transport (non-fickian) which refers to a combination of both diffusion and erosion controlled drug release.

CONCLUSION: The results all the way suggest that lag time is dependent on the nature of the materials employed in plug preparation and found that position of the plug in the capsule body significantly affects lag time. It is proved that an increase in the filler concentration in the plug results in a decrease in lag time. Finally, it is possible to formulate a dosage form release a drug over a desired period of time with specific release rates by manipulating the polymers and their amounts used to prepare plugs. Rapid advancement and newer developments in the field of drug delivery have led to the formulation of the pulsatile drug delivery system, which can be formulated with ease and, provides a significant amount of

therapeutic benefits. It should also be noted that this drug delivery system is still in the early developmental stage within the laboratory walls and much more research can be performed to make it as a practical clinical alternative.

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