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GASTRORETANTIVE SYSTEM OF ATENOLOL USING HPMC K15

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ABSTRACT: Floating matrix tablets of atenolol were prepared to provide sustained drug delivery of atenolol and also to enhance the bioavailability of the drug. Atenolol was chosen as a model drug because it is better absorbed form stomach than the intestine. Tablets were prepared using direct compression technique using HPMC K15, chitosan and carbopol 934P. Drug and polymers were evaluated for compatibility study using differential scanning calorimetry (DSC). Prepared tablets were evaluated for physical parameters viz. hardness, swelling index, thickness, weight variation, buoyancy time. All the tablets were evaluated for *in vitro* release study using pH 1.2 hydrochloric acid buffer as dissolution medium. To analyze the mechanism of drug release from the tablets, the *in vitro* dissolution datas were fitted to zero order, first order, higuchi release model and korsmeyer and peppas model. All the tablets were showing buoyancy time of 24 hr. The results indicated the release of atenolol from the tablets was in controlled fashion. It was observed that the release of drug followed zero order release and controlled by both diffusion and erosion mechanism. The effervescent based floating drug delivery was a promising approach to achieve *in vitro* buoyancy. The addition of gas generating agent sodium bicarbonate was essential to achieve *in vitro* buoyancy. The drug release from the tablets depends upon the nature of gel matrix. It may thus conclude that polymer swelling play an important role in pattern and amount of drug release from the formulation.
KEY WORDS: FDDS, HPMCK15, Aten, CP, CH

INTRODUCTION

Atenolol is a cardioselective beta-1 adrenoceptor blocker devoid of intrinsic sympathomimetic and membrane-stabilizing activity. It is poorly absorbed from the lower GIT. The oral bioavailability of atenolol has been reported to be ~50%. The human jejunal permeability and extent of absorption is also low. Thus, it seems that an increase in GRT may increase the extent of absorption and bioavailability of the drug.[1-3]

Over the last three decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach, including floating systems, swelling and expanding systems, bioadhesive systems, modified shape systems, high-density systems and other delayed gastric emptying devices.

FDDS or hydrodynamically balanced systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system.

Based on this, an attempt was made through this investigation to formulate floating matrix tablet of atenolol using HPMC K15 with different polymers and their combinations. Drug and polymers were evaluated for compatibility study using differential scanning calorimetry (DSC). The prepared tablets were evaluated for physical characteristics such as hardness, weight variation, drug content uniformity, thickness, floating capacity and swelling index. All the tablets were evaluated for in vitro release characteristics.[4,5]

MATERIALS AND METHODS

Materials:

Atenolol (Aten) was received as a gift sample from Medley Pharmaceuticals Ltd, Daman, India. Hydroxypropylmethylcellulose (HK) was received as a gift sample from Colorcon Industries, Goa, India. Sodium bicarbonate, Carbopol 934P (CP) was purchased from S.D. Fine Chem. Ltd, Ahemedabad, India. Chitosan (CH) was purchased from Sigma-Aldrich chemicals, Banglore, India.

Methods:

Compatibility study:

Physical mixture of aten and other polymers were subjected to compatibility study using differential

scanning calorimetry (DSC) (Shimadzu). For DSC the heating rate were kept at 20^0 min^{-1} up to 200^0 min^{-1} to better integrate the information. The flow of argon was kept at 80 ml/min and the thermographs for pure aten, pure HPMC and physical mixture of drug and polymer are shown in fig. 1.

Fabrication of floating matrix tablets:

Aten, HK, CP, CH, and sodium bicarbonate were passed through sieve no. 80 separately. The drug was then mixed with the polymers and other ingredients in the weight proportion and compressed on a ten station tableting machine (Shakti machines) using flat-faced Punch (diameter 12 mm). Formulations are shown in Table 1.[6]

Physical characterization:

The fabricated tablets were characterized for weight variation (citizen balance), hardness (Monsanto hardness tester) and thickness using a dial thickness apparatus.

Buoyancy capacity:

The floating capacity and floating lag time of the tablets were determined using pH 1.2 hydrochloric acid buffer. The time in minutes taken by the tablet to reach the top from the bottom of the container was floating lag time or FLT and the time for which the tablet constantly floats on the surface of the medium was measured as buoyancy time.

Determination of swelling index:

The swelling indices of tablets were determined in pH 1.2 hydrochloric acid buffer at room temperature up to 8 h. The swollen weight of the tablet was determined at predefined time intervals. The swelling index was calculated using equation: $(W_t - W_0 / W_0)*100$. Where W_0 is the initial weight of tablet, and W_t is the weight of tablet at time t.

Moisture uptake study:

Three tablets from each batch were subjected for moisture uptake studies. The tablets were kept in a dessicator containing saturated solution of potassium chloride to maintain 75 ± 5% RH at room temperature. The weight of the tablets were noted down after each 24 hr till the weight remains constant.[7]

***In vitro* release studies:**

The in vitro release studies for all the batches were conducted in USP type II six station dissolution apparatus (tab machines) using pH 1.2 hydrochloric acid buffer as a dissolution medium, at 37 ± 0.5 ^{0}, at 50 rpm and 5 ml aliquots were withdrawn at predetermined intervals and same volume of fresh prewarmed dissolution medium was replaced to maintain sink condition. The absorbances of the aliquots were measured spectrophotomatricaly at 274 nm.[8]

Analysis of in vitro drug release:

To analyze the mechanism of drug release form the tablets, the in vitro dissolution datas were fitted to zero order (K=kt), korsmeyer and peppas model ($F=kt^n$), higuchi ($F=k\sqrt{t}$) release models. Where F is the fraction of drug release, k is the release constant and t is time.[9-11]

RESULTS AND DISCUSSION

Physical mixture of drug and polymer was subjected to DSC for compatibility study and the obtained DSC graphs are shown in fig. 1.

All the tablets were evaluated for various physical properties like swelling index, floating lag time, buoyancy time and moisture uptake. The obtained datas are shown in Table 2 and comparison of swelling index in fig. 2.

Tablets were also evaluated for *in vitro* release study and % Cumulative drug release was calculated. Obtained datas were fitted to zero order (K=kt), korsmeyer and peppas model ($F=kt^n$), higuchi ($F=k\sqrt{t}$) release models. The obtained datas are shown in Table 3 and comparison of dissolution properties in fig. 3.

Compatibility study:

Physical mixture of drug and polymer was analyzed by DSC in order to ascertain if there were any interaction between the active ingredient and the polymer. DSC graphs for the drug and polymer are given in the fig. 1. Which showed that pure drug gives sharp endothermic peak near 160^0, which retained in the physical mixture of drug and polymer also. Thus HPMC K15 had no visible effect on the drug peak. This suggested that drug and polymer were compatible with each other.

***In vitro* buoyancy time:**

Non-effervescent floating drug delivery was used to achieve *in vitro* buoyancy. Initial batches of aten (H1) did not exhibit any buoyancy time. An effervescent approach was then adopted by adding sodium bicarbonate as a gas generating agent (H2 to H6). Sodium bicarbonate induced CO_2 generation in the presence of dissolution medium (pH 1.2 hydrochloric acid buffer). The gas generated is trapped and protected within the gel formed by hydration of polymer, thus decreasing the density of tablet. As the density of tablet falls below 1 the tablet becomes buoyant. The tablets prepared from H1 failed to buoyant, while tablets prepared with gas generating agent show stable and persistent buoyancy (H2 to H6). The results are shown in the Table 2.

Swelling index:

Tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release. Kinetics of swelling is important because the gel barrier is formed with water permeation. Swelling is also a vital factor to ensure floating. To obtain floating the balance between swelling and water acceptance must be restored.[10]

Tablets from H3 and H4 showed significantly higher swelling indices and faster rate of swelling compared with other tablets. The swelling indices are given in Table 2 and results are as shown in fig. 2. Tablets of batch H3 and H4 resulted in higher swelling indices compared to H2. The reason for higher swelling index values appeared to be CP act as channelizing agent, there by it allows more permeation of water into the gel layer and there by it enhances the water retention property of the HK. This could be the reason for more moisture

uptake by tablets of batch H3 and H4. Moisture uptake values are given in Table 2.

***In vitro* dissolution studies:**

Aten's oral bioavailability has been reported to be ~50%. The human jejunal permeability and extent of absorption is also low.[1-3] If the aten dosage form can be retained in the stomach as long as possible, to allow for maximum absorption, aten's bioavailability could be improved. Floating drug delivery system is one approach in it. The GI residence time is prolonged because of the floating behavior. Different swellable polymers like HK, CP and CH were used to prepare the tablets. HK was chosen because it was widely used as low density hydrocolloid systems, upon contact with water, a hydrogel layer would be formed to act as a gel boundary for the delivery system. The release profiles for the tablets from H2 to H6 are shown in fig. 3. It is clear from the figure that release of aten from the tablets showed biphasic release and also there is an initial burst effect. The release of aten from H3 showed ideal biphasic release comprise of initial burst effect to release as an immediate dose from the tablet. After release of the first fraction, the release of the sustained dose follows. The release of aten was increased with presence of CP, CH and their concentrations. Only 67% drug was released from H2, possibly because of the formation of stronger gel matrix. But as the presence of CP and CH along with their concentration influence the release and increased the release of aten from tablets by acting as channelizing agent thereby they made the gel structure more permeable.

Kinetics of drug release:

The dissolution data of all batches were fitted to zero order, first order, Higuchi and Korsemeyer and Peppas equations and it was observed that the release of aten from all the formulations follows the zero order release kinetics. The value of slope for the korsemeyer and peppas model were as shown in Table 3 and indicates that drug release form the tablets were non fickian diffusion and controlled by both diffusion and erosion, the r^2 value of Higuchi's model confirms diffusion.

This study discusses the preparation of floating tablets of aten. The effervescent based floating drug delivery was a promising approach to achieve in vitro buoyancy.

Fabricated tablets showed acceptable weight variation, hardness and uniformity of drug content. The addition of gas generating agent sodium bicarbonate was essential to achieve *in vitro* buoyancy. Addition of channelizing agent CP and CH to tablets prepared by HK (H2 to H6) attributed biphasic release from the tablets. The drug release from the tablets depends upon the nature of gel matrix. It may thus conclude that polymer swelling play an important role in pattern and amount of drug release from the formulation.

Table 1. FORMULATIONS OF TABLET

Batch code	HPMC K15 (mg)	Carbopol 934P (mg)	Chitosan (mg)	Sodium bicarbonate (mg)
H1	250	-	-	-
H2	250	-	-	50
H3	225	25	-	50
H4	200	50	-	50
H5	225	-	25	50
H6	200	-	50	50

*All the tablets contain 25 mg of aten.

Table 2. VARIOUS PHYSICAL PROPERTIES OF TABLETS

Batch Code	Swelling Index (%)*	Lag Time (m)	Buoyancy Time (m)	Moisture Uptake (mg)
H2	158.52 ± 0.34	2 ± 0.27	24 ± 0.4	2.3 ± 0.04
H3	175.43 ± 0.40	3 ± 0.33	24 ± 0.7	12 ± 0.06
H4	206.46 ± 0.28	7 ± 0.21	24 ± 0.5	17 ± 0.03
H5	164.91 ± 0.30	3 ± 0.23	24 ± 0.5	15 ± 0.04
H6	183.23 ± 0.33	3 ± 0.20	24 ± 0.6	9 ± 0.06

* % swelling index at the end of 8 h. Values are means ± SD, n=5.

Table 3. RELEASE ANALYSIS OF TABLETS

Batch Code	% Cumulative Drug Release*	r^2 for Zero Order Equation	n Value for Peppas Equation
H2	67.85 ± 0.25	0.9689	0.7038
H3	76.91 ± 0.36	0.9761	0.6881
H4	71.23 ± 0.42	0.9769	0.633
H5	65.68 ± 0.51	0.9613	0.6278
H6	65.58 ± 0.3	0.9894	0.9263

% Cumulative drug release at the end of 8 h. Values are means ± SD, n=4.

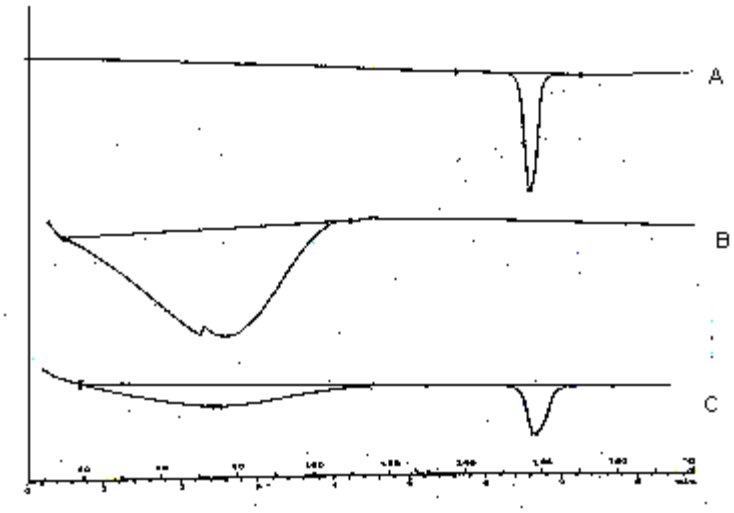

Figure 1: Where A is the DSC for pure drug, B is the DSC for HPMC K15 and C is the DSC for physical mixture of drug and polymer

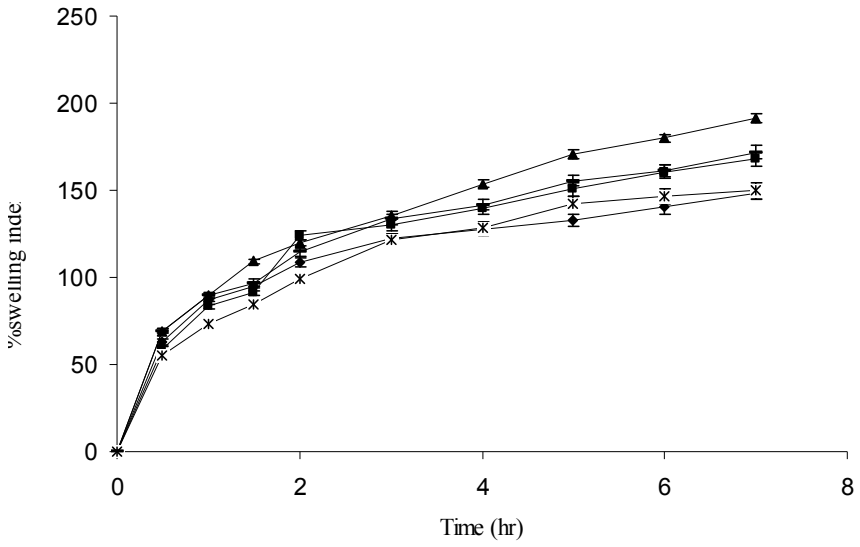

Fig. 2: Comparison of swelling properties of H2 (♦), H3 (■), H4 (▲), H5 (*) and H6(-) (n=5)

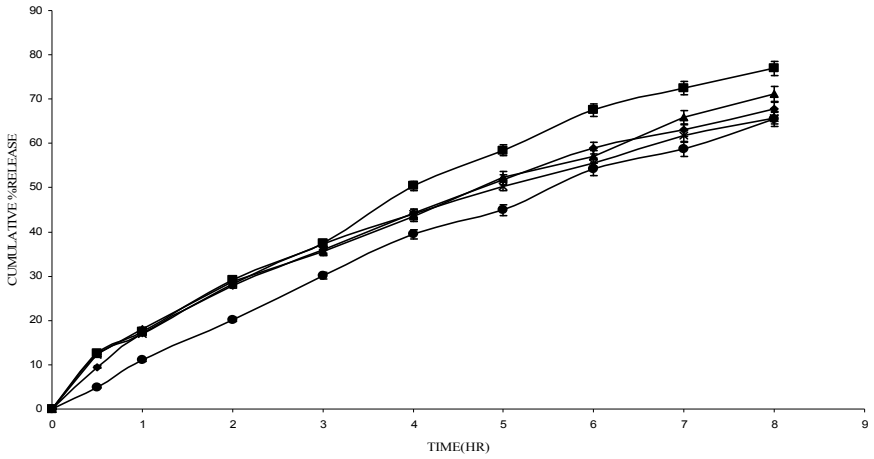

Fig. 3: Comparison of dissolution properties of H2 (♦), H3 (■), H4 (▲), H5 (●) and H6 (*) (n=4)

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