Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2016, 8(8):1190-1198

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Novel gastroretentive mucoadhesive pulsatile tablet for Verapamil hydrochloride

Navya Bhukya and Rajeshri Dhurke*

Department of Pharmaceutics, St. Peter's Institute of Pharmaceutical Sciences, Kakatiya University, Hanamkonda, Warangal 506001, Telangana State, India

ABSTRACT

The aim of the present work was to formulate and evaluate an oral gastro retentive mucoadhesive pulsatile delivery system for treatment of arrhythmias which usually occurs in early morning hours. Gastroretentive mucoadhesive pulsatile tablets (GMP) of verapamil hydrochloride were prepared by compression coating technique using differents ratios of swelling polymers such as HPMC E15 and Carbopol 974P. Various formulations were prepared and evaluated for pre and post compression parameters. Swelling index, mucoadhesive strength and water uptake studies were performed to select an optimum concentration of polymer that would exhibit desired lag time and mucoadhesion time. Drug excipient incompatibility studies were carried out which showed no chemical interaction. From the, in vitro release studies and swelling index studies, it was observed that formulation F7 coated with 380 mg HPMC and 5 mg carbopol 974P showed optimum lag time of 5 h with highest percent drug release of 98.67% at the end of 6th hour. The mucoadhesive strength of 48.3 g as well as the force of adhesion 0.47 N was higher for F7 as compared to other formulations. Formulation F7 showed better mucoadhesion property for a period of 5h which indicated that it would retain in the stomach for desired period. Formulation F7 was considered to be best formulation that can achieve site specific and time release of verapamil hydrochloride to treat arrhythmias effectively.

Keywords: Gastroretentive, verapamil hydrochloride, pulsatile delivery, mucoadhesive tablet, arrhythmia

INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems. This system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time thereby ensuring sustained therapeutic action**.** But there are certain conditions which demand the release of the drug after a lag time when and where it is required [1-3] such a release pattern is known as a pulsatile release. Pulsatile drug delivery is defined as the rapid and transient release of a certain amount of molecules within a short time period immediately after a predetermined off-released period, i.e., lag time. These systems are designed according to the circadian rhythm of the body [4-8].

Gastro retentive drug delivery systems (GRDDS) can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability [9]. Drugs which are easily absorbed from the gastrointestinal tract and those with short half-lives are quickly eliminated from the systemic circulation due to which frequent dosing is required. Gastroretentive drug delivery system provides effective plasma drug concentration for longer periods thereby reducing the dosing frequency is being formulated. It also has an advantage of minimizing the fluctuations in plasma drug concentration by delivering the drug in a controlled and reproducible manner [10-13].

The rationale of the project work was to develop dosage form using the combination of above two approaches i.e Gastro-retentive drug delivery and pulsatile drug delivery. Verapamil hydrochloride is used to treat arrhythmias in

which there is the occurrence of ventricular premature beat with a peak time between 6 am and 12 noon. These two approaches are combined with an aim to retain the dosage form in the stomach for desired time to provide maximum absorption through absorption window and at the same time would release the drug after a predetermined lag time this would help to relieve occurrence of arrhythmias in early morning hours [13-14]. Gastroretentive mucoadhesive pulsatile release tablet would be the best option for achieving site specific and time release verapamil hydrochloride, based on chrono-pharmaceutical approach of arrhythmias.

EXPERIMENTAL SECTION

Materials

Verapamil hydrochloride was procured as a gift sample from Dr. Reddy's Laboratories Hyderabad, India, Carbopol 974 P was a kind gift from Lubrizol India Pvt. Ltd., Hydroxypropyl methyl cellulose (HPMC E 5 and E15) were obtained as gift samples from Colorcon Asia Pvt. Ltd Mumbai, India, Lactose monohydrate, Microcrystalline cellulose were purchased from S.D. Fine Chemicals Pvt. Ltd. Mumbai, India. All other chemicals and reagents used were of analytical grade.

Method

Preparation of core tablets

Verapamil hydrochloride core tablets were prepared by direct compression method. All the ingredients were accurately weighed including drug (80 mg), microcrystalline cellulose (10.2 mg), lactose (40.4 mg) were mixed uniformly. After sufficient mixing lubricants such as magnesium stearate and talc were added and further mixed for additional 2-3 minutes, tablets were then compressed with 8 mm punch using 16 station tablet punching machine (Cadmach Machinery Pvt. Ltd., India). The average weight (135 mg) of the core tablets were kept constant for all formulations (F1-F7) [15-17].

Preparation of gastroretentive mucoadhesive pulsatile release tablets (GMP)

Core tablets containing verapamil hydrochloride were press coated with different ratios of HPMC E15 and Carbopol 974P in two steps. First required amounts of HPMC and carbopol were weighed and mixed uniformly, from this half amount of coating were filled into the die, followed by core tablet in the center of die, this was slightly pressed to fix the coating around and under the core, and the rest of the coating were filled and finally compress to get gastroretentive mucoadhesive pulsatile tablets having 11mm diameter. Formulations for gastroretentive mucoadhesive pulsatile tablets (GMP) are given in table 1.

Table 1: Formulation of verapamil hydrochloride (GMP) tablets

Formulation code	Core tablet weight (mg)	HPMC E15 (mg)	Carbopol 974P (mg)
F1	135	100	5
F2	135	150	5
F3	135	200	5
F4	135	350	3
F5	135	350	5
F6	135	350	8
F7	135	380	5

Drug Excipient incompatibility studies [17-18]

Solid state characterization studies were conducted to rule out the interaction between the drug and excipients in the formulation using FTIR spectrophotometer (IR Prestige 21 Shimadzu, Japan). FTIR studies were done for the pure drug (Verapamil hydrochloride), polymers (HPMC E15, Carbopol 974 P), core tablet and GMP tablets to determine compatibility between drug and excipients. In the case of incompatibility the peaks corresponding to the functional groups in the drug may shift to different wave numbers compared to spectra of the pure drug and pure excipients.

Physical characterization of GMP tablets

The GMP tablets were evaluated for pre and post compression parameters. The physical characteristics such as thickness, hardness, friability, and content uniformity and weight variation tests were evaluated for all the formulations according to the Indian Pharmacopoeia.

In vitro drug release

For core and GMP tablets

Drug release from verapamil hydrochloride core and press coated tablets was determined by using United States Pharmacopoeia (USP) type II (paddle) dissolution apparatus using 0.1N HCl (900 ml) at 37 ± 0.5º C. The speed of rotation was maintained at 50 rpm [15]. Aliquots of dissolution medium were withdrawn at predetermined time

interval and content of verapamil hydrochloride was determined by using UV spectrophotometer (Spectro UV 2080, Double beam, Analytical Technologies, India) at 278 nm. The dissolution studies were conducted in triplicate.

***Ex vivo* mucoadhesion strength** [17, 18, 19]
The mucoadhesive strength of the tablet was measured on the modified physical balance. The apparatus consisted of a modified double beam physical balance in which the right pan was replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. Another glass arrangement of suitable height and diameter was prepared, which was kept in a beaker filled with 0.1N HCl, and then placed on the right side of the balance. Freshly excised goat stomach mucosa was procured form local slaughter house and kept in Krebs buffer during transportation, 0.1N HCl was used as moistening fluid during studies. The underlying mucous membrane was separated carefully using a surgical blade and washed thoroughly with 0.1N HCl. It was then tied over the glass arrangement using a thread. The block was then kept in a glass beaker filled with 0.1N HCl up to the upper surface of the goat stomach mucosa to maintain stomach mucosa viability during the experiments.

To determine adhesion time of developed GMP tablets a simple study was performed using goat stomach mucosa. Freshly obtained goat stomach mucosa was excised by removing any underlying adipose tissue and equilibrated in a Petri plate containing 0.1 N HCl. GMP tablet was carefully placed on mucosa and the time of adhesion was noted from initial of '0' h to 6h.

Force of adhesion and mucoadhesive strength was calculated using following formulae,

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength}}{100} \times 9.81$$

$$\text{Mucoadhesive strength (N/m}^2\text{)} = \frac{\text{Force of adhesion}}{Surface\ area\ of\ tablet}$$

Swelling, Water uptake and Erosion studies [18-21]
Swelling, water uptake and erosion studies were conducted similarly to the *in vitro* dissolution studies using USP Type I (basket) apparatus. At selected time intervals, an individual tablet was withdrawn using the basket and blotted to remove excess of liquid then weighed on an analytical balance. The wetted tablets were then dried in an oven at 105^{o}C for 3h, cooled in desiccators and weighed again. This procedure was repeated until constant weight was achieved (final dry weight). Swelling index and extent of erosion were calculated using the formulae given below

$$\text{Swelling Index (\%)} = \frac{\text{Wt} - \text{Wi}}{W\text{i}} \times 100$$

Where, Wt is the weight of wetted tablet at each time interval and Wi is the initial dry weight of the tablet.
The extent of erosion (E) was determined from

$$\text{E (\%)} = \frac{\text{Wi} - \text{Wf}}{W\text{i}} \times 100$$

Where, Wf is the weight of the dried tablet or partially eroded tablet at each time interval. The increase in weight (uptake) due to absorbed liquid (A) was calculated at each time point from,

$$\text{A (\%)} = \frac{\text{Wt} - \text{Wf}}{W\text{f}} \times 100$$

RESULTS AND DISCUSSION

Drug Excipient incompatibility studies
FTIR spectrum showed all prominent peaks of verapamil hydrochloride which was comparable with standard IR graph as seen in Figure 1. The data indicated that there was no incompatibility between drug and excipients used in the formulations.

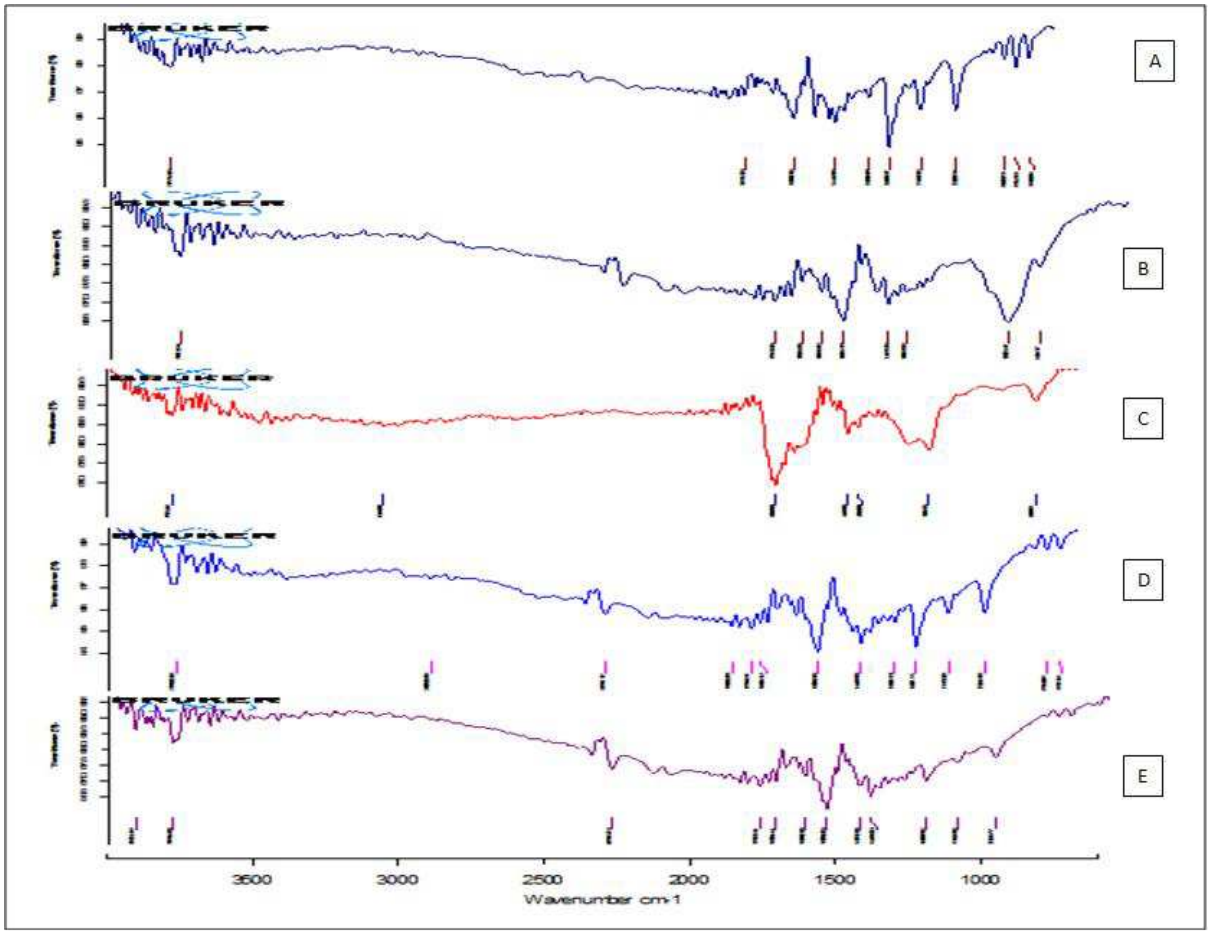

Figure 1: FTIR spectra of A- Verapamil hydrochloride, B-HPMC E15, C- Carbopol 974P, D-Core tablet, E-Formulation

Characterization of pre-compression blend

Powder blends of all formulations were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The angle of repose was less than 25º and Carr's index values were less than 15 for all the batches indicating good to fair flow ability and compressibility. Hausner's ratio was less than 1.3 for all the batches indicating good flow properties.

Evaluation of tablets

The results of hardness, thickness, friability, uniformity of weight and drug content of all the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied within the limits as given in table 2. The friability values were less than 0.81% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 2.0 to 4.83 mm. All the formulations satisfied the content of the drug as they contained 98.1 to 107.0% of verapamil hydrochloride and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control.

Table 2: **Physical evaluation of developed tablets**

Formulation code	Hardness ((kg/cm^2))*	Weight variation (mg)***	Thickness (mm)*	Friability (%)**	Drug Content (%)*
C	2.8±0.9	134.73±1.33	2.0±0.116	0.71±0.03	103.00±1.01
F1	3.5±0.7	234.31±1.09	2.53±0.057	0.81±0.01	99.70±0.28
F2	4.6±0.6	289.48±0.98	2.79±0.057	0.32±0.03	99.50±0.30
F3	5.8±0.2	340.13±1.07	3.5±0.057	0.55±0.06	100.13±1.66
F4	6.2±0.1	487.86±1.64	4.23±0.057	0.19±0.01	99.6±0.32
F5	6.4±0.4	490.50±0.73	4.61±0.115	0.39±0.01	98.13±1.51
F6	6.6±0.3	492.83±1.95	4.83±0.057	0.39±0.02	99.66±0.75
F7	6.5±0.2	517.31±2.19	4.72±0.057	0.34±0.05	100.4±0.55

*All values represent mean ± standard deviation (SD), n=3
** All values represent mean ± standard deviation (SD), n=6
*** All values represent mean ± standard deviation (SD), n=20

***In vitro* drug release studies**

For rapid release core tablets (RRT)

The *in vitro* release graph of rapid release core tablets is shown Figure 2. From the results it is evident that the core tablets showed 100.5± 1.85% drug release within 30 min and found to be suitable to use in pulsatile tablets. As per USP standards verapamil hydrochloride tablets should contain not less than 90% and not more than 110% of the labeled amount of verapamil hydrochloride.

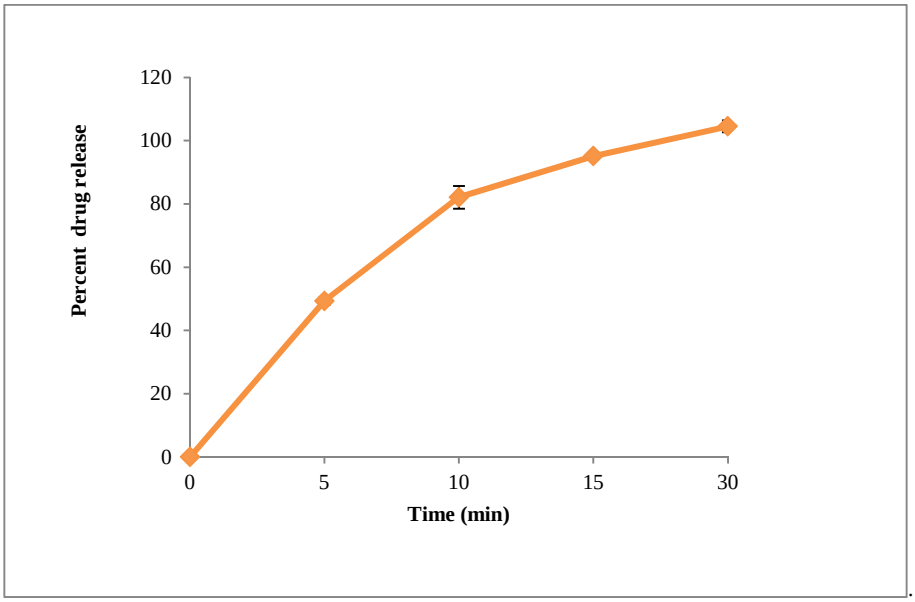

Figure 2: Dissolution profile of Verapamil hydrochloride core tablets

For gastroretentive mucoadhesive pulsatile tablets (GMP)

Core tablets containing verapamil hydrochloride were press-coated with a low-viscosity HPMC grade (HPMC E15) and (Carbopol 934P). *In vitro* release profiles of verapamil hydrochloride coated systems are shown in Figure 3. Seven formulations were designed to have different tablet release profiles by changing weight (100mg- 380mg) of coating layers with HPMC E15 and Carbopol 974P. *In vitro* dissolution studies of all press coated formulations (F1-F7) showed distinct lag time (no release period) after which drug was released. As the concentration of the polymer used in coating layer was increased the lag time was found to increase leading to decreased drug release. The lag time observed in formulation F1, F2, F3 with a polymer concentration of (100 mg HPMC E15 and 5mg Carbopol 974P), (150mg HPMC E15 and 5mg Carbopol 974P), (200 mg HPMC E15 and 5mg Carbopol 974P) were found to be 1 h, 1.5 h and 2 h respectively whereas formulation F4, F5 with polymer concentration of (350 mg HPMC E15-3 mg Carbopol 974P), (350mg HPMC E15 and 5mg Carbopol 974P) gave a lag time of 3 h and 4 h respectively. Formulation F6, F7 with polymer concentration of (350mg HPMC E15 and 8mg Carbopol 974P), (380mg HPMC E15 and 5mg Carbopol 974P) gave the lag time of 4 h, and 5 h respectively. Formulation F1 showed 99.6% drug is release in 2 hours, F2 showed 99.19 % drug release in 3 h, formulation F3, F4 showed 100.1%, 98.33% drug release in 5h, F5 released 97.94 % drug in 6 h, where as F6 and F7 showed 93.21 % , 100.2 % drug release in 7 h respectively.

When GMP tablet was placed in the medium, the hydrophilic polymeric layer started swelling by imbibing the medium and underwent progressive modification in terms of thickness and consistency. In the second phase of the dissolution process, the coating layer gradually eroded to a limiting thickness and finally, a rupture of the shell was observed under the pressure applied by the swelling, releasing drug from core tablets. These overall stages corresponded to a lag time capable of exhibiting a delayed release of the drug. The initial lag time and delay in drug release was highly dependent on the concentration of hydrophilic polymer used for press coating. Increasing the concentration of polymers results in increased in diffusion path length which results `in delayed release of drug. [18, 19, 20, 21]. The lag time of the tablet coated with 380 mg of HPMC E 15 and 5mg carbopol 974P was found to be 5 h so the F7 formulation is selected as optimized formulation.

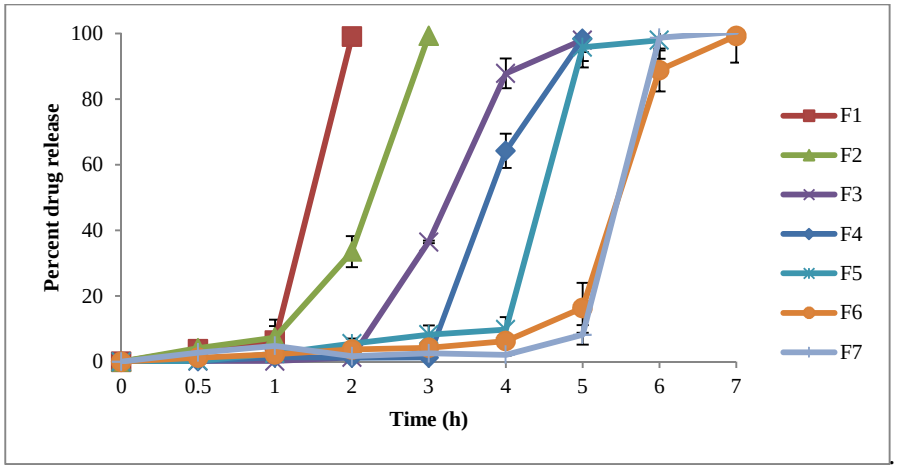

Figure 3: *In vitro* release of verapamil hydrochloride from GMPT coated with different concentrations of HPMC E15 and Carbopol 974P

Swelling and water uptake studies

The swelling studies of gastro retentive mucoadhesive pulsatile tablets containing HPMC E15 and Carbopol 974P with different concentration were performed. Pulsatile tablets containing HPMC E15 and Carbopol 974P at low concentration (200 mg-5mg) showed that the swelling front erodes faster and the swelling front erosion was comparably slower in pulsatile tablets with a higher concentration of HPMC E15 and Carbopol 974P (380mg-5mg) due to their marked viscosity properties. A direct correlation between swelling and lag time was observed and found that the formulations having maximum swelling indices showed higher lag time [19, 20, 21, 22].

The percentage swelling and water uptake of all formulations were shown in figures 4 and 5 Swelling index and water uptake studies were done for five formulations as formulation F1 and F2 eroded very fast. From the results it is evident that formulations F3-F5 showed swelling 48.16±0.92, 49.86±0.25, 51.36 ±1.16% up to 2h and F6 & F7 showed 58.69±2.6, 61.13±0.56 % swelling up to 3rd h then gradually decrease in swelling occurs due to the erosion of the coating layer.

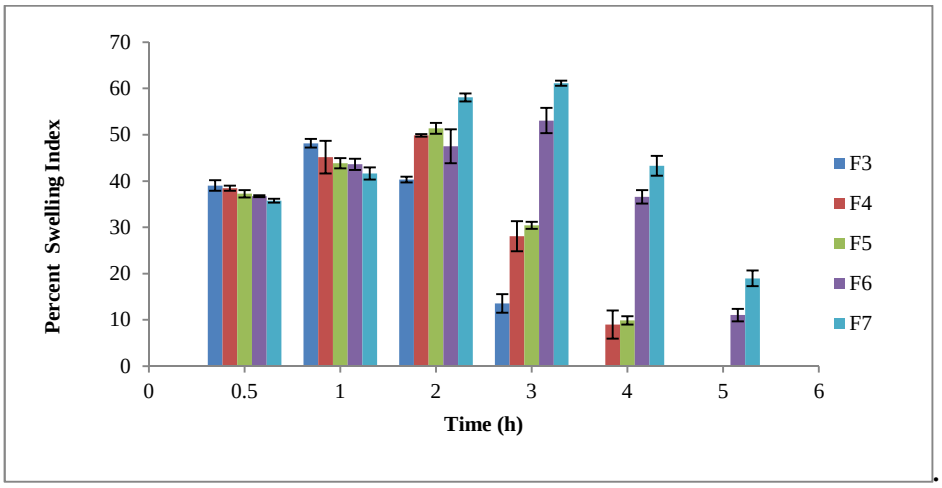

Figure 4: Swelling studies for gastroretentive mucoadhesive pulsatile tablets with different concentrations of HPMCE15 and Carbopol 974P

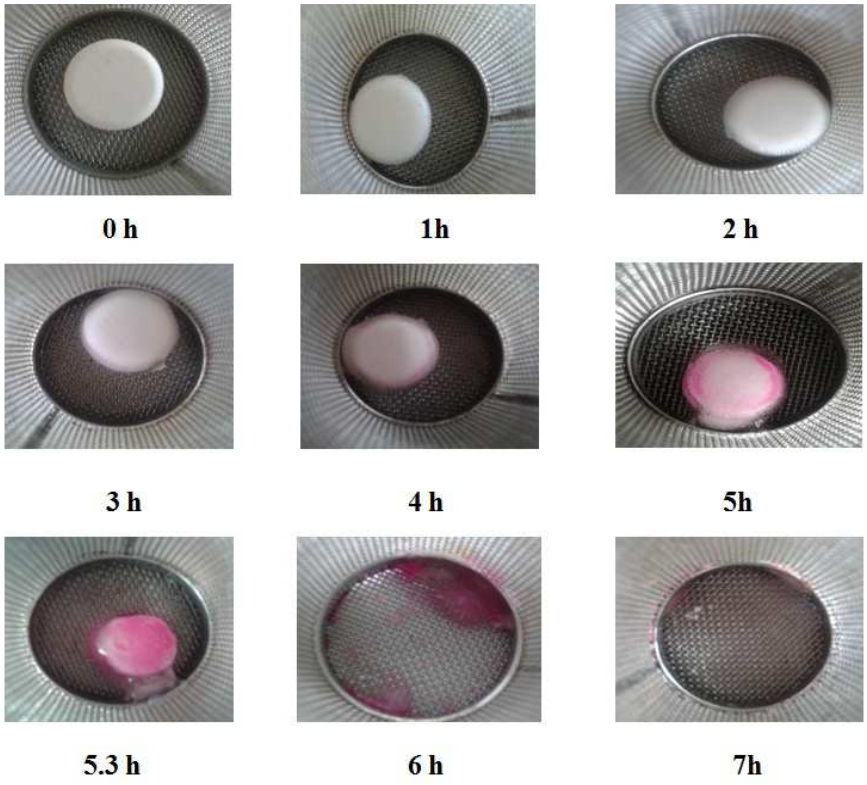

Figure 5: Morphological changes of formulation 7 (F7) during swelling studies

At '0' h the gastroretentive mucoadhesive pulsatile tablet is intact. Tablet swells at its maximum in first 3h. At 4h pink colour of core can be seen from outer press coat. After 5h press coat is completely removed and core tablets starts disintegrating and it release its contents completely after 5.3h.

***Ex vivo* mucoadhesion strength**

Mucoadhesion occurs when mucoadhesive polymers come in contact with water of GI fluids. Polymers imbibe fluid and swell those results in exposure of bioadhesive sites for hydrogen bonding. Hydration also induces mobility in polymer and enhances interpenetration process between polymer and mucin. The mucoadhesive property is mainly affected by the concentration of the polymer used; increase in the concentration of polymers increases the mucoadhesive strength of the formulation [18, 19, 20]. Figure 6 shows mucoadhesive strength and force of adhesion (N) of different formulations. The highest mucoadhesive strength (48.3 g) as well as the highest force of adhesion (0.47 N) was observed with formulation F7 (prepared with 380mg HPMC E15 and 5mg carbopol 974P) compared with other formulations. Formulation F1 and F2 showed very less mucoadhesive strength whereas formulation F3, F4, F5 and F6 showed mucoadhesive strength of 18, 21, 29, 38 g respectively. This mucoadhesive strength (48.3g) would be sufficient enough to retain the dosage form in stomach up to 6 hours the mucoadhesion time for GMP tablets can be seen in figure 7.

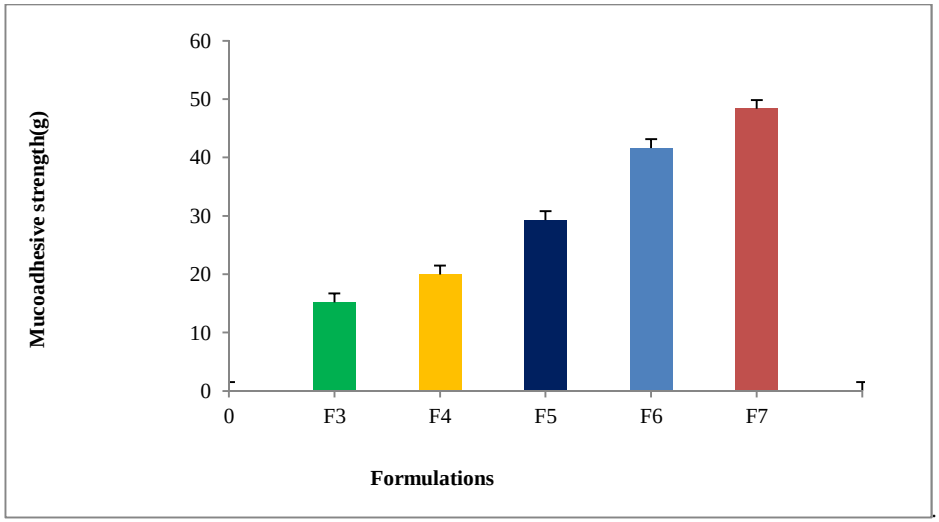

Figure 6: Mucoadhesive strength of GMP tablets with different concentrations of HPMCE15 and Carbopol 974P

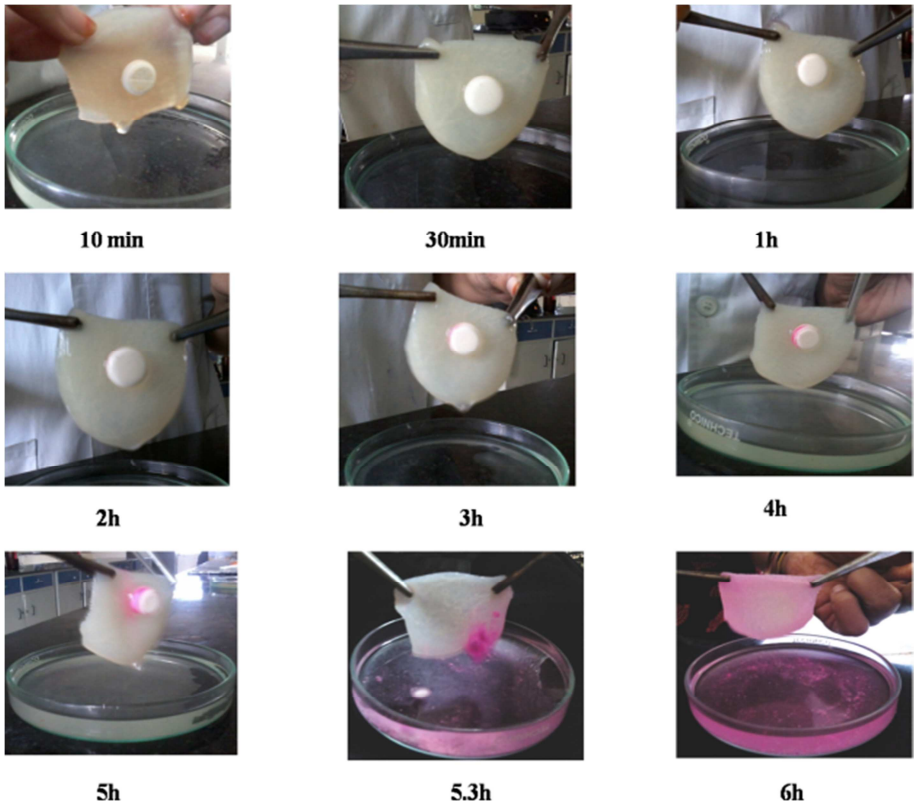

Figure 7: Mucoadhesion time for formulation F7 (380 mg HPMC E15 – 5 mg Carbopol 974P)

CONCLUSION

Gastroretentive mucoadhesive pulsatile tablets of verapamil hydrochloride were successfully developed, taking into consideration the chronotherapy of arrhythmias. Different formulations were developed a varying concentration of HPMC E 15 and Carbopol 974 P in press coating layer. Solid state characterization (FTIR studies) indicated that there was no chemical interaction between drug and polymers. From the swelling studies, water uptake studies and mucoadhesive studies it was evident that GMP tablets (F7) containing 380 mg HPMC E15 and 5mg Carbopol 974P in coating layer gave the desired drug release with a lag time of 5 h and highest mucoadhesive strength (48.3 g) and force of adhesion (0.47 N). Hence this formulation would be helpful for the patients to treat arrhythmias which occur in early morning hours.

Acknowledgements
The authours are thankful to Dr. Reddy's Laboratories Hyderabad and Colorcon Asia Pvt. Ltd Mumbai for providing gift sample of Verapamil hydrochloride and Hydropropyl methyl cellulose polymers respectively.

Conflict of Interest
Authors declare no conflict of interest

REFERENCES

[1] RA Singh; RC Jat; N Sharma; T Rahul, *Int. J. Res. Dev. Pharm. Life Sci.*, **2013**, 2(4), 482-492.
[2] J Ravi Kumar Reddy; MV Jyothsna; TS Mohamed Saleem; C Madhu Sudhana Chetty, *J. Pharma. Sci. Res*., **2009**, 1(4), 109-115.
[3] GS Sharma; MV Srikanth; MU Uhumwangho; KS Phani Kumar; KV Ramana Murthy, *Int. J. Drug Del.*, **2010**, 2, 200-212.
[4] K Satinder; BD Ramandeep; N Vjjwal, *Univ. J. Pharm*., **2013**, 2 (1), 21- 41.
[5] M Krishna; B Semwal; S Neelam; K Ruqsana, *The Pharma. Innov*., **2012**, 1, 5-13.
[6] R Singh, P Kumar; R Malviya. *Eur. J. Biol. Sci*., **2010**; 2 (3), 67-76.
[7] M Srujan Kumar; A Siddiqua; G Thanusha; K Shalini; S Tyagi; J Patel Chirag., *J. Drug Discov. Therap.*, **2013**, 1 (4), 15-22.
[8] A Kumar; S Ranga; *Int. J. Drug Dev. Res*., **2012,** 4(4),97-107.
[9] S Swetha; A Ravi Teja; DV Gowda; *Int. J. Res. Pharma. Biomed. Sci*., **2012**, 3(3): 1285-1293.
[10] M Rajeevkumar; B Satyanarayana; P Nagakanyaka Devi; N Vamsi, S Muddasar; S Irrfan Pasha; S Vemireddy; P Deepthi, *Acta Chemica. Pharma. Indi*., **2013**, 3(2), 149-164.
[11] A Alexander; Ajazuddin; DK Tripathi; T Verma; SJ Maurya; S Patel, *Int. J. Applied Biol. Pharma. Tech*., **2011**, 2(1), 434-445.
[12] M Trivedi Utkarsh; VM Patel; M Ashok; P Mitesh, *Int. J. Inst. Pharm. Life Sci.*, **2011**, 2(1), 1-18.
[13] A Pandey; G Kumar; P Kothiyal; Y Barshiliya, *Asian J. Pharm. Medi. Sci.*,**2012**, 2 (3), 48-54.
[14] A Alexander; S Sharma; Ajazuddin, MD Khan Junaid, Swarna. *Int. J. Res. Ayurv. Pharm.,* **2011** 2(4), 1155-1161.
[15] FC Carvalho; ML Bruschi; RC Evangelista; MP Daflon Gremiao, *Brazilian J. Pharma. Sci.,* **2010**, 46, 2-17.
[16] T Pranshu; K Shaffi; NV Satheesh Madhav, *Int. J. Pharma. Bio. Sci,* **2011,** 2(1), 458-467.
[17] M Chandira; MK Chiranjib; B Jayakar; *Int J PharmTech Res.,* **2009**,1(4), 1663-1667.
[18] VN Deshmukh; JK Jadhav; DM Sakarkar, *Asian J Pharm*, **2009**, 3, 54-58.
[19] VK Ravindran; S Vasa, S Sandhya, B David, B Otili, YM Rao, *Malayasian J. Pharm Sci*., 2012, 10, 61-77
[20] D Ramyasree; E Basanth Babu; D Rajeshri, *Int. J. Pharm. Pharma. Sci*., **2014**, 6(5), 659-664.
[21] GM Khan; Z Jiabi, *Pak. J. Pharma. Sci*., **2000**,13, 33-45.
[22] VS Koppisetti; N Chandra, M Bhagvan Raju, *Int. J. Res. Pharma. Biomedi. Sci.*, **2010**, 1(2) 36.
[23] DK Patel; MR Patel; KR Patel; NM Patel, *American J. Pharmtech. Res.*, **2012**, 2(3), 843-855.