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STUDIES ON DESIGN AND IN VITRO CHARACTERIZATION OF MODEL DRUG ATENOLOL CONTAINING FLOATING TABLETS USING GUAR GUM AND HYDROXY PROPYL METHYL CELLULOSE

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Abstarct *:* The present research study was aimed to develop a floating tablets containing atenolol as a model drug by using natural polysaccharide polymer guar gum (GG) and semi synthetic hydroxyl propyl methyl cellulose (HPMC). The atenolol floating tablets were prepared by direct compression technique based on effervescent approach using sodium bicarbonate as a gas generating agent. The prepared tablets were evaluated for weight variation, hardness, friability, drug content, tablet density, floating lag time, total floating time and in vitro release studies. The effect of combination (1:1) of polymers GG and HPMC proportion on in vitro drug release profile was evaluated. The floating lag time and total floating time of all the formulations were increased by increasing polymers concentration. The formulations containing sodium bicarbonate 40 mg per tablet showed desired buoyancy. The in vitro studies revealed that, the atenolol release could be sustained up to 24h by increasing the proportion of GG:HPMC mixture. Further, the floating tablet containing 35% of mixture of HPMC (17.50%) and GG (17.50%) in the ratio 1:1 with an average tablet weight of 400mg released 98.23% at the end of 24 hours was found to be suitable for successfully sustaining the atenolol release upto 24h in physiological environment of stomach and to improve the patient compliance. The FTIR studies confirms that there is no interaction between drug and tablet excipients.

Key words: Floating drug delivery system, sustained release, guar gum, antihypertensive and atenolol.

I. INTRODUCTION:

Rapid gastrointestinal transit could result in incomplete drug release from the device above the absorption zone leading to diminished efficacy of the administered dose. Therefore, different approaches have been proposed to retain the dosage form in the stomach. Gastroretentive drug delivery systems are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal tract[1]. A modified release drug delivery system with prolonged residence time in the stomach is of particular interest for drugs- acting locally in the stomach; having an absorption window in the stomach or in the upper part of small intestine; those unstable in the intestinal or colonic environments; or those having low solubility at high pH values (Shailesh et al.2011, Dehghan et al.2009).

To formulate a successful gastroretentive drug delivery system, several techniques are currently used such as floating drug delivery system, low density systems, raft systems incorporating alginate gel, bioadhesive or mucoadhesive systems, high density systems, superporous hydrogel and magnetic system. Among these, the floating dosage forms have been most commonly used (Rocca et al.2003).

Floating drug delivery systems have a bulk density less than gastric fluids and so 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 the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased gastric retention time and control of the fluctuation in plasma drug concentration (Mathur et al. 2010 Shah et al.2009 and Jain et al.2017).

Atenolol, a cardioselective beta-1 adrenoceptor is devoid of intrinsic sympathomimetic and membrane stabilizing activity. It belongs to the category of antihypertensive agents and helps in reducing high blood pressure. Atenolol is also included in the treatment of angina and cardiac arrhythmia. It has absorption window in the upper GIT whereas the poor absorption in lower GIT. This varied absorption results in lowering bioavailability i.e. 50% with a halflife of 6-8 h. Thus it seems that increase in gastric residence time may increase the extent of absorption and bioavailability of drug (Gorde et al.2012, Delima et al.1995, Mayavanshi et al.2008, Jelvehgari et al.2010). A gastric floating drug delivery system (GFDDS) can overcome at least some of these problems and is particularly useful for drugs that are primarily absorbed in the stomach. The GFDDS is able to prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug. Therefore, in the present study it was aimed to design gastroretentive floating tablets of atenolol by using natural (GG) and synthetic polymer HPMC as tablet matrix formers, sodium bicarbonate as gas generating agent and to characterize its floating ability and drug release behavior.

II. MATERIALS AND METHODS

Materials:

Atenolol was obtained as gift sample from Natco Pharma, Hyderabad, India. ltd., Bangalore, India as a gift sample. Guar gum and MCC were procured from SD fine chemicals , Mumbai, India. HPMCK15M was received as a gift sample from Colorcon Asia pvt. Ltd. Goa, India. Sodium bicarbonate, Magnesium stearate and talc (SDF fine chemicals ltd.), were obtained from the local market. All other chemicals used were of analytical grade and used as received without any further purification or modification.

Evaluation of Powder flow properties:

Before compression the powder bed materials which is ready for compression (after adding glidant and lubricant) were evaluated for various flow properties like repose angle, compressibility index and hausner ratio by adopting standard techniques (Lachman et al.1970 and Rosa et al.1994).

A. Angle of repose: The angle of repose was determined by fixed funnel method. A funnel was kept vertically in a stand at a specified height above a paper place on a horizontal surface. The funnel was closed and a granule was filled in funnel. Then funnel was opened to release the granules on the paper to form a smooth conical heap. The height and radius of heap was measured and the angle of repose was calculated by using the following formula.

$$Ø = \tan^{-1} h/r$$

Where Ø = Angle of repose, h =height of heap and r = radius.

B. Bulk Density: A known amount of granules was transferred in to a 25-ml measuring cylindrical carefully level the granules without compacting and measure the bulk volume. The bulk density was determined by using the formula;

Bulk density = Weight of granules/ bulk volume

C. Tapped Density: Tapped density was determined by digital bulk density apparatus. A known amount of granules was transferred into the measuring cylinder and tapped up to 100 times and measure the tapped volume. The tapped density was determined by using the formula.

Tapped Density = Weight of granules / tapped volume

D. Compressibility Index: The compressibility index was calculated by using following formula.

Compressibility Index = [Tapped density- Bulk density / Tapped density] ×100

E. Hausner's ratio: The hausner's ratio was calculated by using following formula.

Hausner ratio = Tapped density / bulk density

Preparation of floating tablets containing atenolol:

The floating tablets of atenolol as a model drug (average weight 400mg) based on effervescent approach using sodium bicarbonate as a gas generating agent was prepared by direct compression formula (Table I) by using a mixture of natural biodegradable polysaccharide material guar gum and time dependent hydrophilic swellable polymer HPMC K15M in different proportions, MCC (Avicel) as a direct compression aid. All the ingredients were accurately weighed and thoroughly mixed in a glass mortar by pestle and spatula for 20 min and passed through the mesh (150 µm) to ensure complete mixing of all the ingredients. The resulting powder blend was then lubricated (1% talc and 2% magnesium stearate) and compressed into tablets using 8mm round, flat and plain punches on a single station tableting machine (Cadmach, India). The compression force was adjusted to obtain tablets with hardness in range of 4-5 Kg/cm^2.

Physical evaluation tests for floating tablets:

The developed atenolol gastroretentive floating tablets were tested for various standard physical tests and average values calculated. Weight variation was determined by weighing 20 tablets individually, and the average weight and percent deviation of each tablet was calculated. Hardness was determined by taking 5 tablets from each batch using a Monsanto hardness tester and the average pressure ($kgcm^2$) applied to crush the tablet was determined. Thickness (n=5) by using screw guage. Friability was tested on ten tablets by first weighing and then placing them in a Roche

Friabilator, which rotated for 4 min or 100 revolutions. After dusting, the total remaining mass of the tablets was recorded and the percent friability calculated (Lachman *et al*., and Rosa *et al*.,).

Tablet Density: Tablet density is an important parameter for floating tablets. The tablet will float when its density is less than that of 0.1N HCL (1.004g/cm^3). The density was determined using following formula (Mathur et al.2010 Shah et al.2009).

$$V = \pi r^2 h$$
$$d = m/v$$

Where;

v = volume of tablet (cc), r = radius of tablet (cm), h = crown thickness of tablet (cm) and

m = mass of tablet

The tablet contacts the test medium, tablet expanded (because of swellable polymers) and there was liberation of CO_2 gas (because of effervescent agent, $NaHCO_3$). The density decreased due to this expansion and upward force of CO_2 gas generation. This plays important role in ensuring the floating capability of the dosage form.

In- vitro buoyancy studies: The in vitro buoyancy was determined by floating lag time and total floating time as per the method described by Rosa *et al*. The tablets (n = 3) were placed in 1000 ml of 0.01N simulated Hydrochloric acid, as per USP. The time required for the tablets to rise to the surface and float, was determined as floating lag time. The duration of time the dosage form constantly remained on the surface was determined as the total floating time (Mathur et al.2010 Shah et al.2009).

Estimation of drug content: The atenolol floating tablets were tested for their drug content to ensure uniformity in drug content. The 05 tablets were weighed individually and finely powdered. The powder weight equivalent to 100 mg of drug atenolol was weighed and placed in a 100 mL stoppard volumetric flasks containing 50 mL of pH 1.2 buffer solution to extract the drug and allowed to stand for 4 hour with intermittent vigorous shaking to ensure complete extraction of the drug. The solution then made up to 100 mL with pH 1.2 buffer solution and mixed thoroughly. The solution was filtered, diluted and drug content was estimated at the λ_{max} 224 nm by UV-spectrophotometer (Shimadzu, Japan).

In-vitro dissolution studies: The ability of GG and HPMC based atenolol floating tablets to sustain the drug in stomach environment was assessed by in vitro drug release studies (n = 3) by using USP XXIII dissolution testing apparatus (50 rpm and 37 ± 0.5^{o}C) in 900 mL pH 1.2 buffer solution. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at predetermined time intervals (1, 2, 3, 6, 9, 12, 15, 18 and 24 hours) and the samples were replaced with fresh dissolution medium. The sample were filtered (0.45µ nylon membrane filter), suitably diluted and analyzed for percentage of drug release by UV spectrophotometer at the λ_{max} 224 nm.

FTIR spectral studies: The incompatibility or any chemical interaction between the model drug (atenolol) under investigation and matrix materials or other excipients used in the preparation of floating tablets was assessed by fourier transform infrared (FTIR) studies. The KBr pellets with neat drug atenolol, powdered floating tablet formulation of optimized batch (selected on the basis of in vitro drug release studies) before storage, after storage and placebo tablet formulation of optimized batch were prepared. A FTIR (Shimadzu, FTIR 8400S, Japan) spectrophotometer was used to record IR spectra of the prepared pellets in the range of 400-4000 cm^{-1} with a resolution of 1 cm^{-1} to confirm the absence of chemical interaction of atenolol with excipients of floating tablets.

Stability studies: To assess the long term stability of the compression coated tablet formulations, the optimized batch formulation (AHG35) were stored at 40 ± 2 o C/75 ± 5% RH for a period of three months. Samples were observed for any physical change, compressional characteristics and drug content. At the end of three months storage study period, the initial (zero time) results were compared with post-stability testing period results (Mathews et al. 1999). The powdered samples of atenolol floating tablet formulations AHG35 were also subjected to FTIR studies.

III. RESULTS AND DISCUSSIONSS

Powder flow properties:

Angle of Repose (θ): The values obtained for angle of repose for all the formulations are tabulated in Table 2. The values were found to be in the range of 24.97^0 to 27.92^0 indicating powder materials have good flow property.

Compressibility Index: The tapped and untapped density of all the formulation was less than 1 and a Carr's compressibility index of less than 16 % (Table 2) and therefore it was ascertained that, the powder bed is compressible indicating that the powder have the required flow property for compression.

Hausner's ratio: The value of this was found between 1.18 and 1.23 indicating that the powder showed satisfactory results and good flow property (Table 2).

3.3. Physical evaluation of atenolol floating tablets: The atenolol floating tablets of all the batches were produced under similar conditions to avoid the influence of any processing variables. The developed floating tablets of different tablet batch formulations were subjected to various evaluation tests such as hardness (tablet strength), friability and weight deviation by using standard procedures. In a weight variation test, the pharmacopoeia limit for the percentage deviation for the tablet mass of more than 400mg is ± 5%. The weight variation of the floating tablets was found between 1.85% and 4.02%. The percentage weight deviations were found to be within the limits, and hence all tablet formulations passed the test for uniformity of weight as per official requirements. The hardness of the floating tablets was found to be in the range of 5.14 ± 0.15 to 5.54 ± 0.30 kg/cm^2 indicating that the tablets are of adequate strength. Another important parameter for measurement of tablet's strength is friability. The conventional compressed tablets that lose less than 1% of their original weight are generally considered acceptable. In the present study, the percentage friability of floating tablets of all the batches was found to be less than 0.5%, indicating that the friability is within the limits. Values of the hardness test and percent friability indicate good handling properties of the prepared matrix floating tablets. The drug content uniformity ranged from 98.33 ± 3.66 to 100.86 ± 1.39% which ensures uniformity in drug content in all the coated formulations. The results of compressional characteristics (Table 3) for floating tablets containing atenolol showed acceptable pharmacotechnical properties and complied with the in-house specification (falls within the limits of Indian pharmacopoeia) for weight variation, hardness and friability.

Tablet Density: To provide good floating behavior in the stomach, the density of the designed tablet device should be less than that of the gastric contents (1.004 g/cm^3). The density of all the batches of floating tablet was in the range 0768 to 0.862 g/cm^3 which are less than that of gastric fluid (1.004 g/cm^3) as shown in table 4.

Floating Lag Time (FLT) or Buoyancy Lag Time (BLT): The one of the important criteria or requirement of the gastro retentive floating tablet is immediate floating of the tablet in the stomach fluid. In our previous studies (data not shown), the tablet formulations containing GG and LBG (in our previous lab studies, data not shown) alone as a matrix material fails to float, whereas floating tablet formulations containing HPMC alone as a

matrix material has shown good buoyancy lag time (22 to 49sec) but formulation failed to sustain the release of drug in the testing fluid for a testing period of 24h. Therefore, further studies on these formulations have been not done. The floating lag time of all other formulations containing combination of polymers (GG and HPMC) was found to be in the range of 23 sec to 118 sec (Table 4). The floating lag time increases as proportion of polymers increases in the tablet formulations. This may be due to the high density of polymers, hindering the fast hydration of the matrix.

Floating ability or Total Floating Time (TFLT): This is another important requirement of the gastro retentive floating tablet, that the tablet should remain floatable for a minimum period of 24h to sustain the drug release and to minimize the frequency of drug administration. The floating ability of prepared tablets was evaluated along with dissolution studies. The total floating time of formulations were found to be in the range of 10 to >24 h (Table 4). The tablets with low proportion of polymer (GG/HPMC) contents float immediately in 0.1N HCl (pH 1.2) as compared to tablets with high proportion of polymer.

Drug content Uniformity: The drug content of the entire floating tablet batch formulations were found to be in the range 98.83 ± 4.66 to 100.82 ± 2.86% indicating that the prepared floating tablets contain stated amount of atenolol drug for a dose of 100mg floating tablets of 400mg.

In vitro drug release studies: In novel gastroretentive floating tablets containing 100mg of atenolol were prepared with a mixture of natural biodegradable polysaccharide polymer guar gum and hydrophilic swellable polymer hydroxy propyl methyl cellulose (HPMC) as matrix materials in the different proportion (5, 10, 15, 20, 25, 30, 35, 40 and 45%) in the ratio 1:1 with a tablet weight of 400mg. To study the effect of polymer concentrations over drug release, HPMC and GG mixture were used in various proportions. The result of in vitro dissolution studies (Fig.1 and 2) shows that the drug release can be reduced by increasing the concentration of GG:HPMC polymers. The results of this study are consistent with which showed that the presence of a highly water-soluble compound (drug) in a HPMC matrix generates an additional osmotic gradient, thereby resulting in a faster rate of polymer swelling and large increase in gel thickness. At higher polymer loading, the viscosity of the gel matrix is increased which results in a decrease in the effective diffusion coefficient of the drug and hence decreased drug release into the dissolution medium.

The release of atenolol in all the formulations with a high proportion of GG fails to release drug completely at the end of 24h in stomach fluid and percent drug release was decreased as the proportion of GG in the floating tablet increases. It was evident from in vitro data that the amount of GG in tablet formulation had significant effect on sustain release of atenolol. The sustained release of drug atenolol upto 24 h from developed formulation was directly proportional to amount of GG rather than on HPMC used in the floating tablets.

The floating tablets containing 5%, 10%, 15%, 20%, and 25% of HPMC:GG mixture in then ratio 1:1 released 99.28, 98.66, 99.02, 98.71 and 99.18% of drug at the end of 8-16h dissolution studies in pH 1.2 buffer solution. The drug release was found to be complete from all the formulations but fails to sustain the drug release up to 24h. The floating tablet formulation containing 5%, 10% and 15% of HPMC: GG mixture released around 90% of the drug in 8h. This might be due to low proportion of polymer mixture present in the floating matrix tablet might not be sufficient to form a viscous gel matrix to sustain the drug release from the tablets. From in vitro release data it is clear that as the proportion of polymer mixture increases the sustained effect of drug release from the device also increased, therefore the polymer proportion in the floating tablet formulation was further increased with an increment of 5%. The floating tablets containing 30% and 35% of HPMC:GG mixture released 99.84% at the end of 20h, where as formulation AHG35 released 98.23% of drug at the end of 24h. The formulation AHG40 and AHG45% has shown a drug release of 90.14 and 86.32 in 24h. From the in vitro release profile data (Figure 2 and 3), it was clear that as the proportion of polymeric matrix material increases, the release rate was decreased, but drug release sustaining effect was increased.

Further, the in vitro release data revealed that for complete and sustaining the drug release upto 24h from floating tablet in the physiological environment of stomach, it should contain 35% of mixture of HPMC and GG in the ratio 1:1, which gave the best sustained release profile (99.23% in 24 hour).

Drug-excipients compatibility (FTIR) studies: The compatability between drug and excipients were tested by FTIR studies. The scanning range used was 4400 to 400 cm^{-1}. The IR Spectra of pure drug atenolol and the formulation blend are compared. The IR spectrum of the pure drug atenolol (Fig. 3A) displayed characteristic peaks at 3400 cm^{-1} and 1645 cm^{-1} due to N-H and C=O amide groups respectively. The peaks of 1245 cm^{-1} and 2900 cm^{-1} are due to alkyl aryl ether linkage and alcoholic –OH groups, respectively. All the above characteristic peaks were also found in the IR spectrum of the formulation AHG35 (peaks at 3350 cm^{-1} and 1650 cm^{-1} due to -NH and = O stretching, respectively and peaks at 1249 cm^{-1} and 2980 cm^{-1} are due to alkyl aryl ether linkage and alcoholic –OH groups respectively (Figure 3B)). The presence of above peaks confirms undisturbed structure of drug in the above optimized floating tablet formulation. Hence, the drug and polymers or excipients used in the floating tablets are considered to be compatible.

Stability studies: Stability studies conducted on the optimized tablet batch formulation AHG35 according to ICH guidelines at 40^0C / 75 % RH for 03 months indicates that there is no significant change in the physical appearancecompressional characteristics and no decrease in drug content (97.28 ± 3.16). No significant difference in the percent drug released (94.13 ± 4.10) from the optimized batch formulation before and after syorage period of three months indicating the formulation could provide a better shelf life during its storage. The IR spectrum of the optimized batch formulation AHG35 (Fig. 3C) after storage period of 3 months shows all the characteristic peaks related to drug indicating no interaction between drug and polymers or excipients.

IV. CONCLUSION:

Based on the results of in vitro drug release studies, the 35% mixture of HPMC (17.50%) and GG (17.50%) in the ratio 1:1 with an average tablet weight of 400mg was found to be suitable for successfully sustaining (up to 24h) and ensuring almost complete release (98.23%) of atenolol in physiological environment of stomach to improve the patient compliance.

Table 1: COMPOSITION OF FLOATING TABLETS CONTAINING MODEL DRUG ATENOLOL.

INGREDIENTS (mg/tablet)	ATENOLOL FLOATING TABLETS FORMULATION CODES								
	AHG05	AHG10	AHG15	AHG20	AHG25	AHG30	AHG35	AHG40	AHG45
DRUG	100	100	100	100	100	100	100	100	100
HPMC K15	20	30	40	50	60	70	80	90	100
Guar gum	20	30	40	50	60	70	80	90	100
Sodium Bicarbonate	40	40	40	40	40	40	40	40	40
MCC (Avicel)	208	188	168	148	128	108	88	68	48
TALC	4	4	4	4	4	4	4	4	4
Magnesium staerate	8	8	8	8	8	8	8	8	8
Total weight (mg)	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**

Table 2: Flow properties of tablet powder blend ready for compression

Powder Batch Codes	Angle of Repose* (θ)	Carr's Index* (%)	Hausner's ratio
AHG5	26.28^0	15.13	1.23
AHG10	25.73^0	15.68	1.16
AHG15	27.92^0	14.52	1.24
AHG20	24.97	13.42	1.18
AHG25	26.18^0	13.37	1.23
AHG30	25.24	13.06	1.20
AHG35	25.92^0	14.82	1.19
AHG40	26.82	14.12	1.21
AHG45	26.82^0	15.44	1.19

Table 3. Compressional Characteristics of Atenolol Floating Tablets.

Tablet Codes	Diameter (mm ± SD)	Thickness* (mm ± SD)	Hardness* (Kg/cm^2 ± SD)	Friability (%)	Drug Content* (% ± SD)	Weight Variation (± %)
AHG5	8.16 ± 0.10	3.62 ± 0.16	5.14 ± 0.15	0.432	99.66 ± 1.63	± 3.46
AHG10	8.12 ± 0.05	3.61 ± 0.18	5.22 ± 0.35	0.509	99.12 ± 2.63	± 4.02
AHG15	8.10 ± 0.12	3.32 ± 0.32	5.16 ± 0.33	0.437	100.82 ± 2.86	± 3.12
AHG20	8.14 ± 0.11	3.22 ± 0.28	5.54 ± 0.30	0.357	98.83 ± 4.66	± 2.28
AHG25	8.08 ± 0.06	3.42 ± 0.27	5.16 ± 0.33	0.287	99.66 ± 3.82	± 3.37
AHG30	8.14 ± 0.40	3.53 ± 0.14	5.52 ± 0.34	0.416	98.33 ± 3.66	± 1.85
AHG35	8.12 ± 0.01	3.63 ± 0.26	5.34 ± 0.34	0.344	98.69 ± 1.63	± 2.82
AHG40	8.16 ± 0.12	3.42 ± 0.12	5.24 ± 0.35	0.408	100.86 ± 1.39	± 3.95
AHG45	8.12 ± 0.05	3.14 ± 016	5.16 ± 0.34	0.537	98.42 ± 2.62	± 2.53

Table 4: Tablet density, Buoyancy Lag Time and Total Floating Time

Tablet Batch Codes	Tablet Density (gm/cc)	Buoyancy Lag Time (Sec ± SD)	Total Floating Time (hr ± SD)
AHG5	0768	23	10
AHG10	0782	26	12
AHG15	0.786	34	12
AHG20	0.793	38	>12
AHG25	0.845	48	>16
AHG30	0.862	72	>20
AHG35	0.856	84	>24
AHG40	0.832	92	>24
AHG45	0.842	118	>24

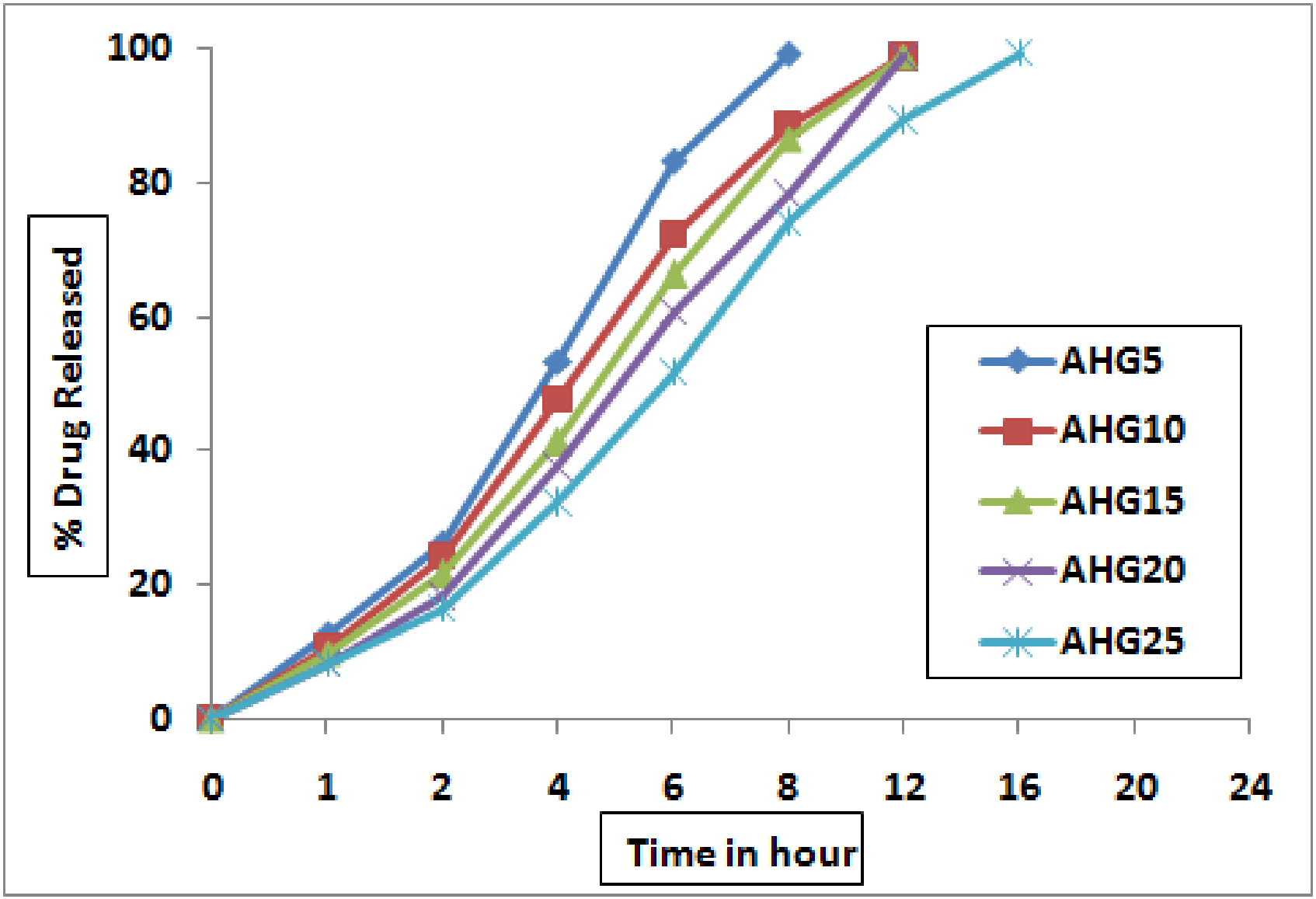

Figure 1: In vitro release profile of atenolol from floating tablets AHG5, AHG10, AHG15, AHG20 and AHG25.

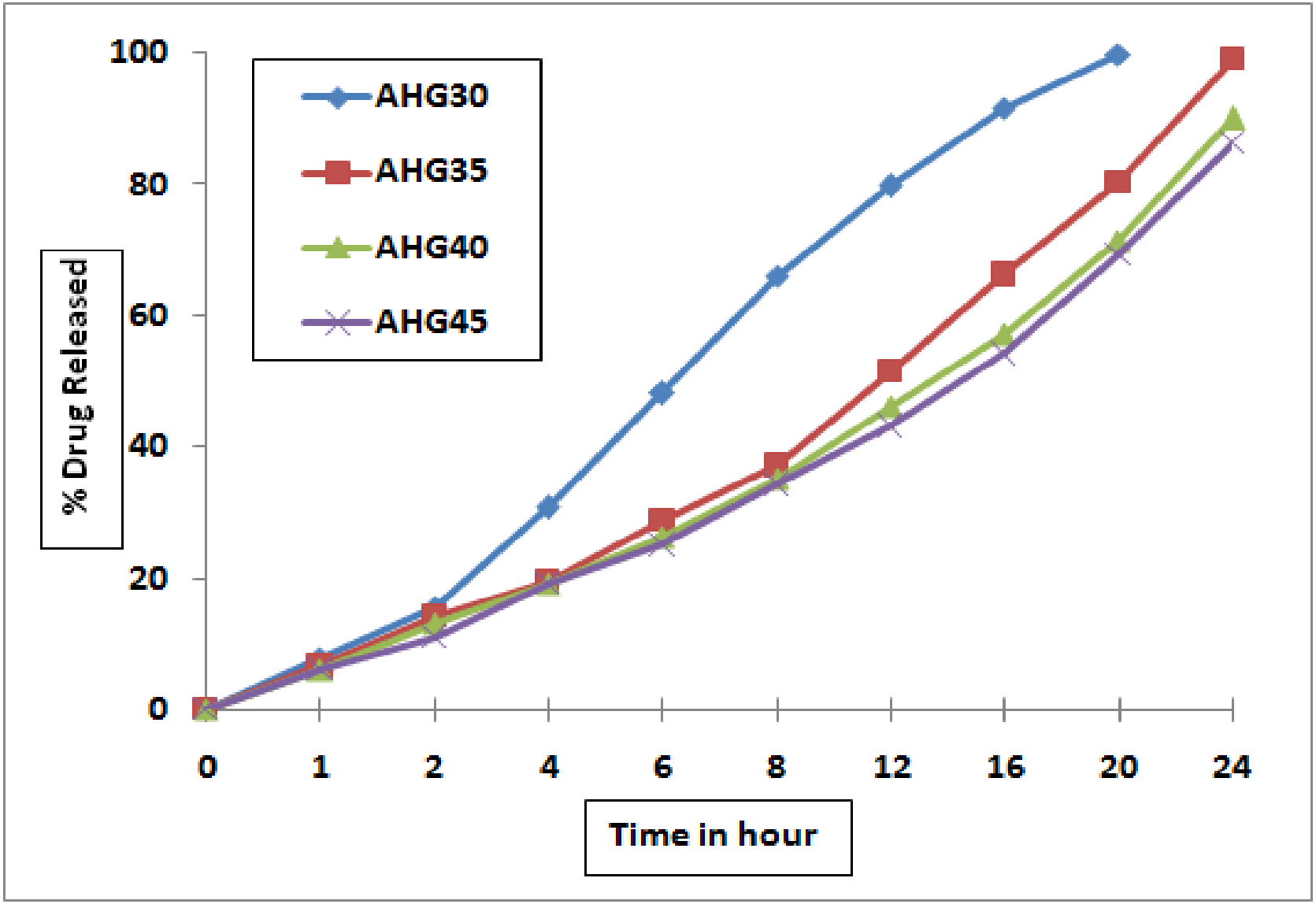

Figure 2: In vitro release profile of atenolol from floating tablets AHG30, AHG35, AHG40 and AHG45.

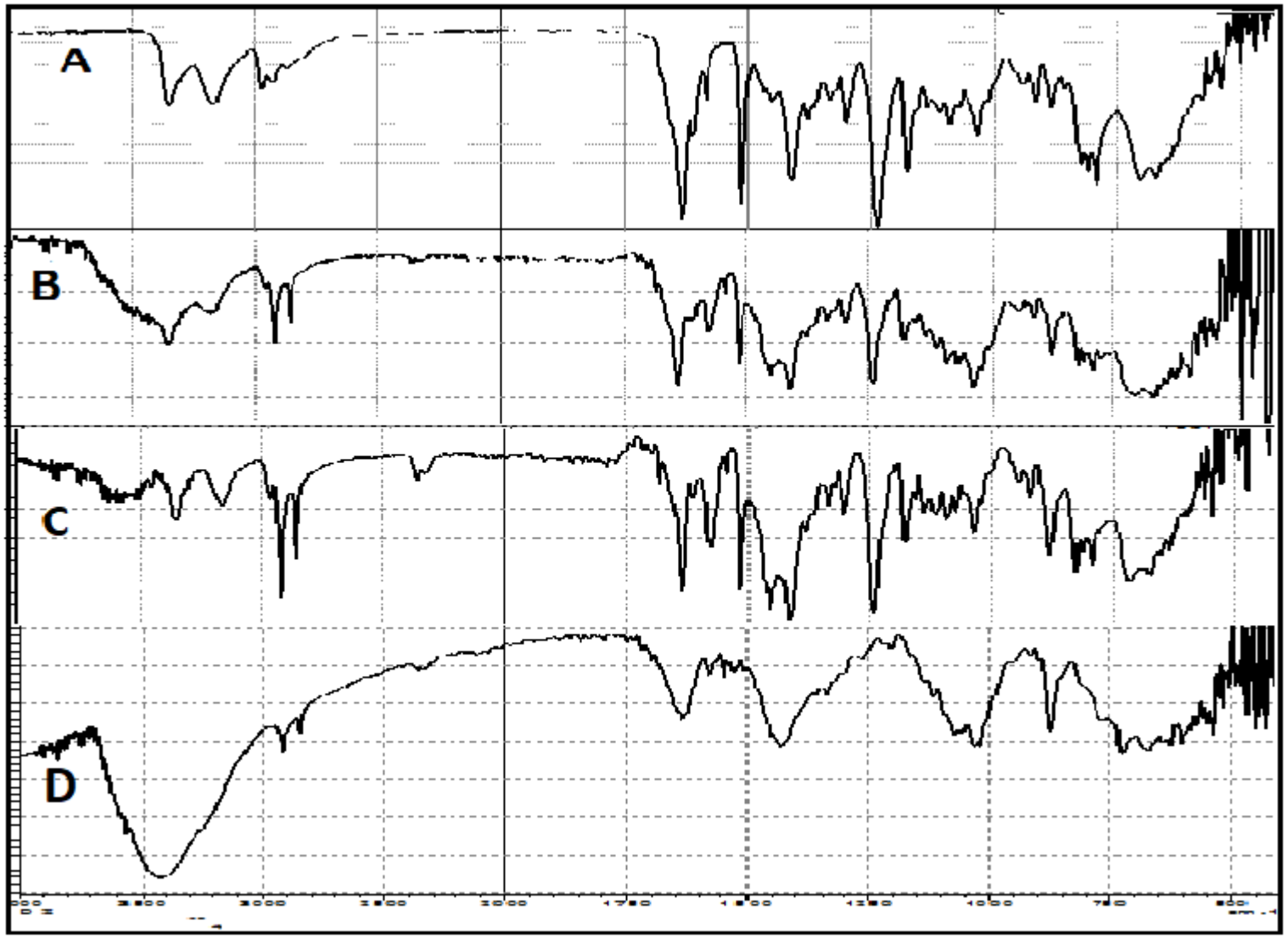

Figure 3. FTIR spectra of neat drug atenolol (A), optimized formulation AHG35 before storage (B), Optimized formulation AHG35 after storage (C) and placebo formulation (D).

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VI. REFERENCES:

1. Shailesh Prajapatia, Laxmanbhai. Patelb and Chhaganbhai Patelb. 2011. Floating Matrix Tablets of Domperidone Formulation and Optimization Using Simplex Lattice Design. Iranian Journal of Pharmaceutical Research, 10 (3): 447-455
2. Dehghan MH, Khan FN.2009. Gastroretentive drug delivery systems: A patent perspective. Int J Health Res. 2:23–44.
3. Rocca JG, Omidian H, Shah K. 2003. Progress in gastroretentive drug delivery systems. Business briefing. Pharma Tech. 5:152–6.
4. Mathur P, Saroha K, Syan N, Verma S, Kumar V. 2010. Floating drug delivery systems: An innovative acceptable approach in gastroretentive drug delivery. Arch Apll Sci Res. 2:257-270.
5. Shah SH, Patel JK, Patel NV. 2009. Stomach specific floating drug delivery system: A review. Int J Pharm Tech Res.1:623-633.
6. Jain NK.2017. Introduction to novel drug delivery system, Vallabh prakashan , Delhi, Second edition, 39.
7. Gorde N. K, Pawar H.A, Khutle K and Chaudhari Y. (2012) ormulation development and optimization of floating microballoons for oral delivery of domperidone," *International Journal of Pharmaceutical and Phytopharmacological Research*, 2(2)101–108.
8. Delima L.G, Kharasch E.D, Butler S. 1995. Successful pharmacologic treatment of massive atenolol overdose: sequential hemodynamics and plasma atenolol concentrations. *Anesthesiology*. 83 (1): 204–207.
9. Mayavanshi A.V and Gajjar S.S.2008. Floating drug delivery systems to increase gastric retention of drugs: a review," Research Journal of Pharmacy and Technology, 345–348.
10. Rocca J.G, Omidian H, Shah K. 2003. Progress in gastroretentive drug delivery systems. *Business briefing. Pharma Tech.,* 5:152–6.
11. Jelvehgari M., Maghsoodi M and emati H. (2010), Development of theophylline floating microballoons using cellulose acetate butyrate and/or Eudragit RL 100 polymers with different permeability characteristics, Research in Pharmaceutical Sciences, 5(1), 29–39.
12. Dehghan M.H, Khan F.N. 2009. Gastroretentive drug delivery systems: A patent perspective. *Int J Health Res*., 2:23–44.
13. Lachman, L, Lieberman H and Kaning J. 1970. The Theory and Practice of Industrial Pharmacy. 3rd ed., Lei & Feiberger, Philadelphia. 283-285.
14. Rosa M, Zia H and Rhodes T. 1994. Dosing and testing invitro of a bioadhesive and floating drug delivery system for oral application. Int. J. Pharm. 105: 65-70.
15. Mathews B.R. 1999. Regulatory aspects of stability testing in Europe. Drug Dev. Ind. Pharm.25,831-856.