



Formulation and Evaluation of Sustained Release Floating Pellets of Amlodipine Besylate

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ABSTRACT

The aim of the present study is to design and develop sustained release pellets formulations for Amlodipine besylate. Amlodipine is an oral antihypertensive agent, commonly used as calcium channel blocker for treating high blood pressure. It is frequently used to treat heart diseases like angina pectoris. The dose of Amlodipine in case of hypertension or angina initially 5 mg daily later adjusted to 10 mg daily by oral route. Amlodipine has a maximum solubility in acidic pH. Amlodipine has a high bioavailability ranging from 60 to 80 % and slow rate of elimination. Amlodipine besylate at different drug to polymer ratios were prepared by extrusion and spheronization technique. The influence of the proportion of the polymer on the release rate of the drug from the pellets was studied. The in-vitro release studies of pellets were carried out in 0.1N HCl for 12 hours. The studies indicated that the drug release can be modulated by varying the concentration of the polymer. Pellets were prepared and evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. Formulation was optimized on the basis of acceptable pellet properties and in-vitro drug release. The resulting formulation produced robust pellets with acceptable drug content and low friability. The release data was fitted to various mathematical models such as, Higuchi, Korsmeyer- Peppas, First-order and Zero-order to evaluate the kinetics and mechanism of the drug release.

Keywords: Sustained release, Ethyl cellulose, HPMC, Pellets, Amlodipine besylate

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INTRODUCTION

Extrusion spheronization is a multiple process of wet mass extrusion followed by spheronization to produce uniform size spherical particles, called as spheroids, pellets, beads or matrix pellets depending upon the material as well as process used for extrusion spheronization.^[1] Extrusion Spheronization has been used in agrochemicals, detergent additives, sweeteners, food and now it is used in pharmaceuticals. Extrusion spheronization is primarily used for the production of multi particulates for oral controlled drug delivery system.

MATERIALS AND METHOD

Amlodipine besylate was obtained from Yarrow chem, Mumbai, HPMC K100M from EID Parry India Ltd, HPMC K15M from Venamax Organics Pvt Ltd, HPMC E15M from Spansules Formulations, Hyderabad, and Citric acid from Triveni interchem pvt. Ltd, Gujarat, Isopropyl alcohol from Spansules formulations, Hyderabad, Ethyl cellulose from Alpha chemika, Mumbai, Starch from Alpha chemika, Mumbai, Micro crystalline Cellulose from Alpha chemika, Mumbai, Talc from alpha chemical Mumbai.

Table I: Composition of Amlodipine besylate Sustained Release floating pellets Prepared with Different Release polymers.

Ingredients (mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Amlodipine besylate	10	10	10	10	10	10	10	10	10
Sodium Bicarbonate	35	35	35	35	35	35	35	35	35
HPMC K100M	21	30	34	----	-----	-----	-----	-----	-----
HPMC K15M	-----	----	-----	34	51	61	-----	-----	-----
HPMC E15	-----	----	-----	-----	-----	-----	34	51	61.2
Ethyl cellulose	10	10	10	10	10	10	10	10	10
MCC	54.6	44.4	41	41	24	13.8	41	24	13.8
Citric acid	10	10	10	10	10	10	10	10	10
Starch	30	30	30	30	30	30	30	30	30
Iso propyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Method of preparation sustained release floating pellets of Amlodipine besylate sustained release floating pellets:

Amlodipine besylate sustained release floating pellets were prepared by a laboratory scale mini extrusion and spheronization technique

Preparation of wet mass

The batch size taken for preparation is equal to 20 doses. Table 1 showing the values for a single dose. All the ingredients of sustained release pellets were passed through the sieve no 100 and weighed according To the formulation. Ingredients were blended for 10 min. solvent isopropyl alcohol was then added to the powder mixture and the mass was kneaded for 10 min of time.

Finally the dry powder was made into dough mass.

Extrusion

The wet powder mass was immediately extruded at 25 rpm through a radial screen with a 1mm aperture screen.

Spheronization

A radial plate spheronizer with a plate diameter (12cm) was used. The friction plate speed in the spheronizer was maintained at 1200 rpm. The was spheronized for 35 min. the wet pellets were dried in a hot air oven at 40° c For 12 hours and then stored in desiccator

EVALUATION OF PELLETS

Determination of bulk density and tapped density

An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V_0) was measured. Then the graduated cylinder was set into the density determination apparatus. The density apparatus was set for 100 taps and after that, the volume was measured. The bulk density, and tapped density were calculated using the formulae

Bulk density = Mass of the pellets/ Bulk volume

Tapped density = Mass of the pellets / Tapped volume

Compressibility index ^[6]

The bulk density and tapped density was measured and compressibility index was calculated using the formula.

% compressibility index = $[(\rho_t - \rho_b) / \rho_t] \times 100$

Where, ρ_t = tapped density, ρ_b = bulk density

Hausner's Ratio ^[7]

Hausner's ratio was determined as the ratio between the tapped density to that of the bulk density

Hausner's ratio = ρ_t / ρ_b ρ_t = tapped density. ρ_b = bulk density.

Flow property

Flow property reflects suitability of material during filling operation. Also it reflects changes in particle size, shape, density, electrostatic charges and adsorbed moisture, which may arise from processing or formulation changes. The more commonly used method to assess flow properties is angle of repose. It is best suited for particles having size above 150 μ m.

Angle of Repose

When bulk granular materials are poured onto a horizontal surface, a conical pile will form. The internal angle between the surface of the pile and the horizontal surface is known as the angle of

repose and is related to the density, surface area and shapes of the particles, and the coefficient of the material. Material with a low angle of repose forms flatter piles than material with a high angle of repose ($\tan \theta$).

$$\tan \theta = h/r$$

Where, h =height of the heap, r = radius of the base of the heap.

Friability and Hardness^[8,9]

It is necessary to attain acceptable friability of pellets that can withstand handling, shipping, storage and operations like coating and filling. Friability is strongly effected by type and amount of binder used. It is affected by method of processing.

Friability is generally determined by use of Roche friabilator. It involves placing measured weight of pellets in the friabilator and rotating it for a predetermined number of revolutions and then measuring the weight of intact pellets. The difference in weight is expressed as percentage.

Drug release kinetics

Various mathematical equations have been proposed for kinetic analysis of drug release from the evaluated formulations. The zero order rate Eq.1 describes the systems where the drug release is independent of its concentration. The first order rate Eq. 2 describes drug release from systems where the release is concentration dependent. According to the Higuchi model Eq. 3, drug release from the insoluble matrix is directly proportional to the square root of time and is based on Fickian diffusion:

$$A_t = A_0 - K_0t \dots\dots\dots (1)$$

$$\log C = \log C_0 - K_1t / 2.303 \dots\dots\dots (2)$$

$$Q = K_2t^{1/2} \dots\dots\dots (3)$$

Where, A_t is the amount of drug released at time t , A_0 is the initial amount of drug in the Pellets and k_0 and k_1 are release rate constants for the zero order and first order respectively. In order to define a model that will represent a better fit for the formulations, dissolution data can be further analyzed by the Peppas's and Korsmeyer's equation:

$$\log M_t/M_a = \log K + n \log t \dots\dots\dots (4)$$

Where, M_t corresponds to the amount of drug released at time t , K is the constant incorporating the structural and geometrical characteristics of the drug / polymer system. And n is the diffusion exponent related to the mechanism of the release.

RESULTS AND DISCUSSION

Discussion on FT-IR

FT-IR spectrum of Amlodipine besylate showed in Figure I, drug polymer interaction was

checked by comparing the IR spectra of the formulation with the IR spectra of the pure drug. There was no significant change in the functional groups between the IR spectra of the pure drug and also no additional peaks were seen in the selected formulation. This confirms that no interaction between drug and excipients.

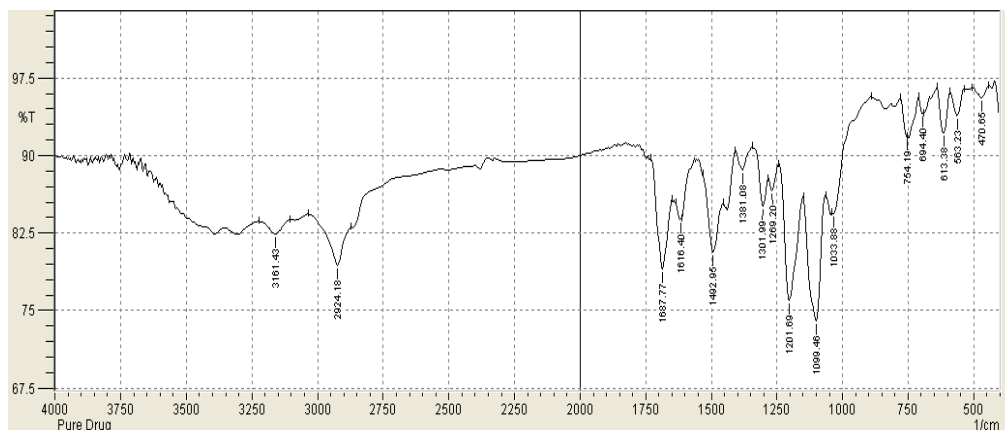


Figure 1: FTIR Spectroscopy of pure drug (Amlodipine besylate).

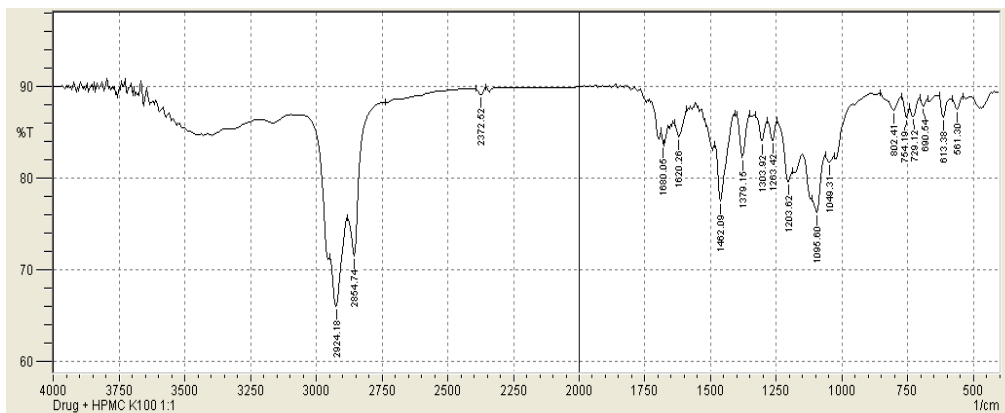


Figure 2: FTIR Spectroscopy of HPMC K100+Amlodipine besylate

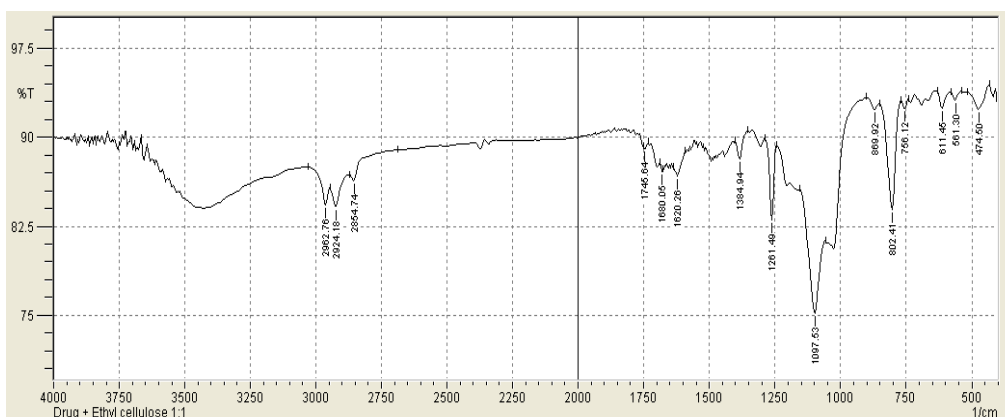


Figure 3: FTIR Spectroscopy Ethyl Cellulose + Amlodipine besylate.

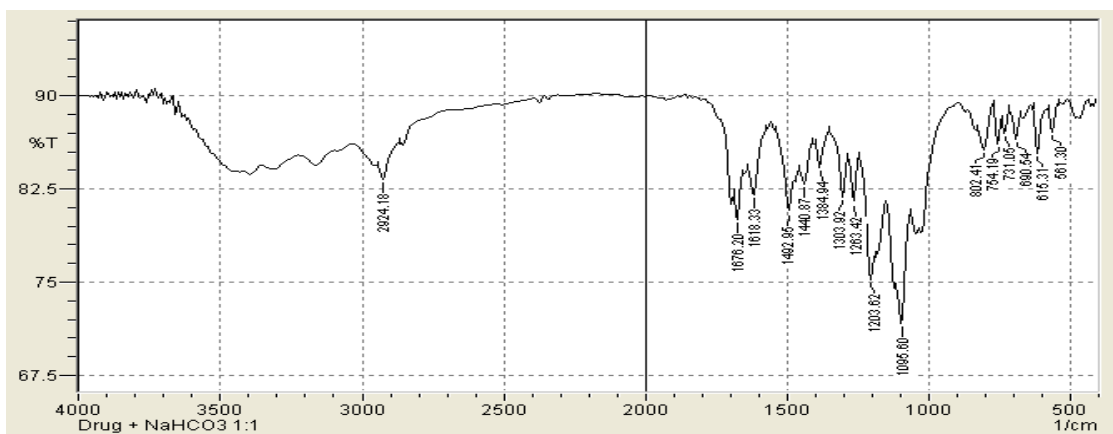


Figure 4: FTIR Spectroscopy of NaHCO₃+Amlodipine besylate

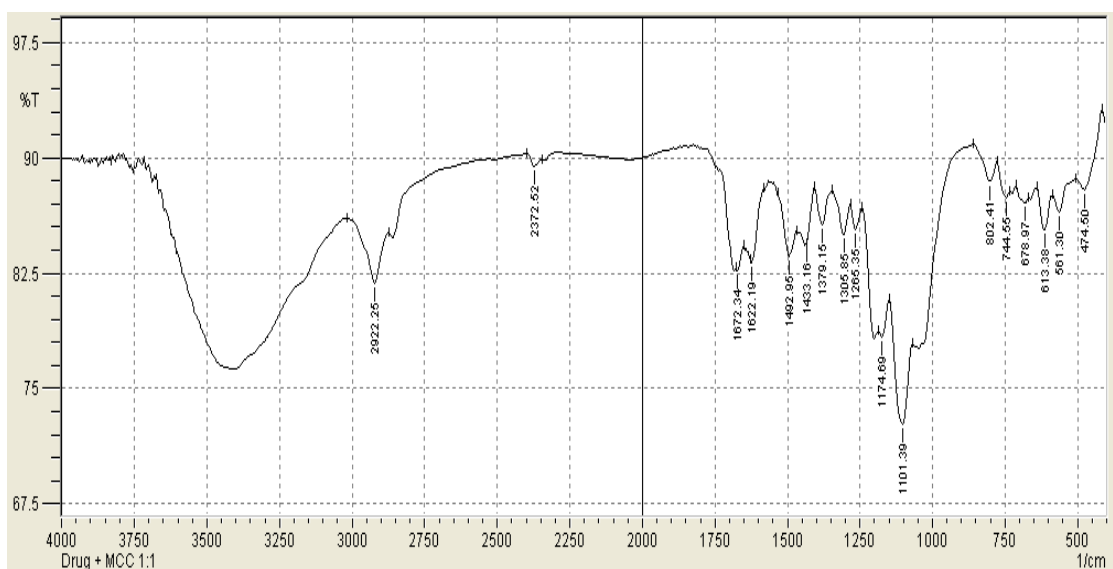


Figure 5: FTIR Spectroscopy of MCC + Amlodipine besylate

Characterization of pellets

Pellets are prepared were evaluated for their flow properties, the results were shown in Table III. Angle of repose was in the range 20.81° to 24.12°, which indicates excellent flow of the pellet formulations. The bulk density of the pellet formulation was in the range of 0.382 to 0.311 gm/cc, the tapped density was in the range of 0.341 to 0.428 gm/cc, which indicates that the powder was not bulky. The Carr's index was found to be in the range of 9.67 to 9.87 indicating compressibility of the tablet blend is good. These values indicate that the prepared granules exhibited good flow properties.

Table II: Data for blend evaluation of formulation (F1 to F9).

Formulation	Bulk density	Tapped density	Carr's index(%)	Hausner's Ratio	Angle of repose
F1	0.382	0.428	9.87	1.093	20.81°
F2	0.284	0.316	10.11	1.118	21.69°
F3	0.291	0.325	9.80	1.097	21.93°

F4	0.310	0.334	10.73	1.120	23.14°
F5	0.277	0.303	11.24	1.099	22.69°
F6	0.304	0.341	10.76	1.117	22.34°
F7	0.293	0.327	9.04	1.130	22.06°
F8	0.318	0.338	10.15	1.126	23.89°
F9	0.311	0.341	9.67	1.119	24.12°

In-Vitro Release Study

In-vitro release studies were carried out for all the formulations as per USP XXII Tablet dissolution tester employing paddle at 100rpm. The In-vitro release study of Amlodipine was conducted for twelve hour in 0.1N HCl of pH 1.2. The results were assessed for 12 hours. The pellets of different formulations were assessed for friability, drug-content, loss on drying and in-vitro dissolution. The results of all the formulations for different tests found to be within the limits. Good uniformity in drug content was found among different batches of pellets and the percentage of drug content is more than 99%. The dissolution test was carried out for all the formulations. F1 release was found to 92% at 12 hours which is due to the concentration of polymer. The further formulations F2 to F9 was prepared by changing the grades of polymers along with different concentration. Formulation F2 to F9 drug release was in the range of 37.29% to 39.31% at the end of 12 hours. F1 formulation was found to be greater release of drug were the ratio of drug and polymer concentration used in 1:1 proportion.

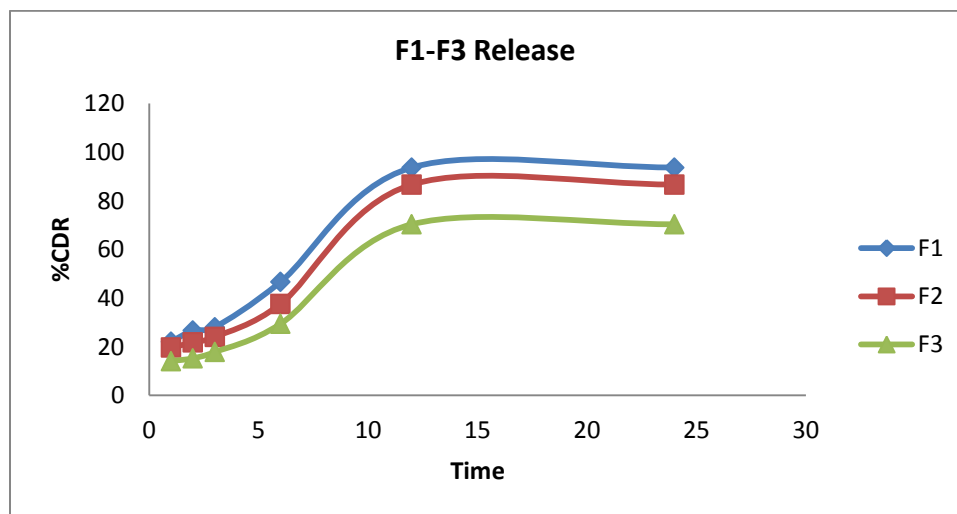


Figure 6: *In-vitro* Dissolution Profile Release Study of Amlodipine besylate floating pellets (F1 to F3) Formulation.

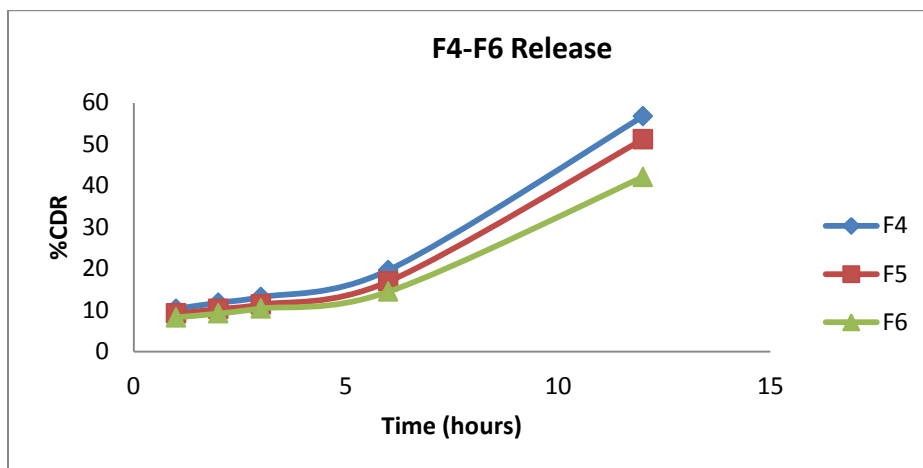


Figure 7: *In-vitro* Dissolution Profile Release Study of Amlodipine besylate pellets (F4 to F6) Formulation.

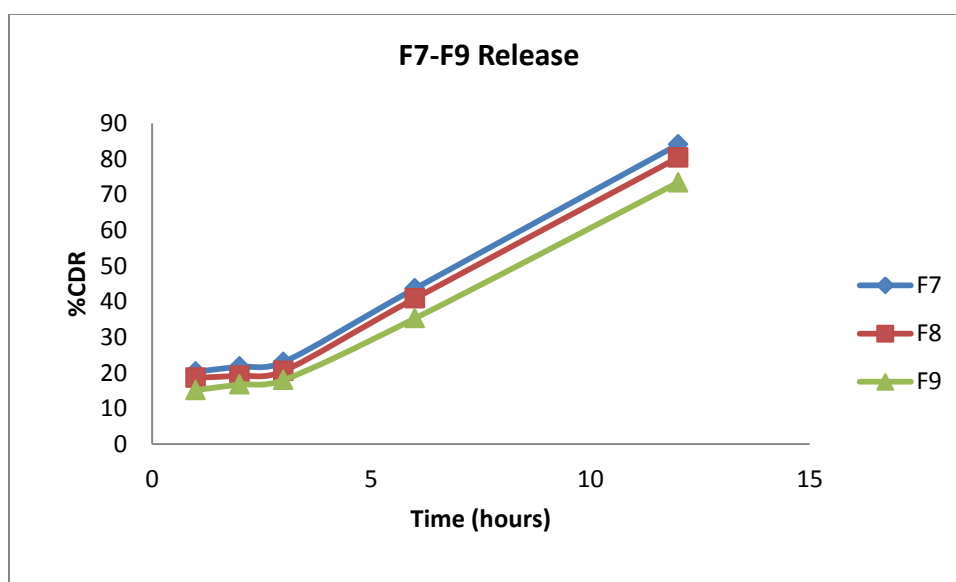


Figure 8: *In-vitro* Dissolution Profile Release Study of Amlodipine besylate pellets (F4 to F6) Formulation.

Drug release kinetics

The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetic data of all formulations F-1 to F-9 might be stated by First order equation as the plots showed uppermost linearity (R^2 : 0.008 to 0.949), than zero order release kinetics (R^2 : 0.004 to 0.935). The "n" values obtained from Korsmeyer Peppas plots range from (-0.1456 to 0.3421) designate that mechanism of release of formulations F-1 to F-9 was found to be Quasi-Fickian diffusion.

Table III: Release kinetic Data of the formulation from F1 to F9.

Formulations	Zero	First	Higuchi	Peppas	N
	Order	Order			
	R ²	R ²	R ²	R ²	
F1	0.990	0.982	0.990	0.990	0.1498
F2	0.467	0.457	0.5831	0.7126	0.1893
F3	0.389	0.363	0.4836	0.6631	0.3421
F4	0.004	0.019	0.0707	0.1407	0.0333
F5	0.016	0.013	0.0584	0.1685	0.0782
F6	0.331	0.307	0.4154	0.5506	0.1331
F7	0.935	0.949	0.9815	0.9971	0.0233
F8	0.009	0.008	0.0251	0.0536	0.0109
F9	0.451	0.449	0.5558	0.6664	0.1456

CONCLUSION

In this study sustained release pellets of Amlodipine Besylate was prepared by extrusion and spheronization technique, using different grades of HPMC like K100M, K15M, E15 as polymers alone as retardant. It was found that increase in the concentration in polymeric ratio decreases the drug release and able to sustain for 12 hours. The formulation F1 containing HPMC K100M showed good drug release over a period of 24 hours and in-turn the release was found to be within the limits specified in monograph. The entire pellet formulations showed acceptable quality control properties like moisture content, loss on drying, drug content uniformity etc. and complied with in the specifications for tested parameters. Thus, formulation F-1 was found to be the most promising formulation on the basis of acceptable pellets properties. The kinetic treatment of selected optimized formulation shows that the regression coefficient for first-order kinetics were found to be higher when compared with those of the zero-order kinetics, indicating that drug release from all the formulations followed first-order kinetics and the n -value lies between -0.1456 to 0.3421 (Korsmeyer-Peppas model) demonstrating that the mechanism controlling the drug release of formulations F-1 to F-9 was Quasi-Fickian diffusion. Therefore, the results of the kinetic study obtained permit us to conclude that an orally sustained Amlodipine besylate pellets delivers the drug through a complex mixture of diffusion, swelling and erosion. Based on the FT-IR studies, there appears to be no possibility of interaction between Amlodipine Besylate and polymers/ other excipients used in the pellets.

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