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FORMULATION AND EVALUATION OF AMLODIPINE BESYLATE OSMOTIC TABLETS

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ABSTRACT

Osmotically controlled oral drug delivery systems utilize osmotic pressure as the energy source for the controlled delivery of drugs thereby, it is possible to achieve and sustain a drug plasma concentration within the therapeutic window, which reduces the side effects and frequency of administration. The present work was aimed to formulate and evaluate osmotic pump delivery system of Amlodipine Besylate using two osmogens (NaCl and KCl) by wet granulation method. The osmogens used in this study did not alter the physicochemical properties of drug, as tested by FTIR. Prior to compression, the prepared granules were evaluated for flow and compression characteristics. After compression, the tablets were evaluated for thickness, hardness, weight variation, friability, percentage of weight gain, drug content, and *in vitro* release studies. The tablets were further coated and evaluation of coated tablets were performed and compared with uncoated tablets. The percentage of weight gain after coating was found to be between 5.57-7.11%. The drug content in the coated as well as uncoated tablets was found to be within the prescribed limits. A slow drug release was observed in coated tablets compared to uncoated formulations. In conclusion, Amlodipine Besylate may be successfully formulated as elementary osmotic pump tablets to provide a control release of drug upto 24 hours.

KEYWORDS: Amlodipine Besylate, osmotic pressure, coated tablets, control release.

INTRODUCTION

The basic rationale of controlled drug delivery system is to optimize the biopharmaceutical, pharmacokinetics and pharmacodynamic properties of drug in such a way that its therapeutic utility is maximized.[1] Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action. Among Oral controlled drug delivery system, Osmotically Controlled Release Systems plays a major role. Osmotic pressure has been used extensively in the fabrication of these drug delivery system. Osmotic drug delivery system differs from diffusion based systems in the delivery of the active agents in driven by an osmotic gradient rather than the concentration of drug in the device.[2] In osmotic drug delivery system,it is possible to achieve and sustain a drug plasma concentration within the therapeutic window of drugs, which reduces the side effects and frequency of administration.[3,4] Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system.[5] Osmotic Pump Tablet (OPT) generally consist of a core including the drug, an osmotic agent, other excipients and semi permeable membrane coat.[6]

Amlodipine Besylate is selected as a model drug in the preparation of osmotic pump tablets. Amlodipine is an antihypertensive agent.[7] It also act as a vasodilator agent, calcium channel blockers, and anti- anginal agents. The conventional marketed product of Amlodipine Besylate tablet released more than 80% of the drug within 90minutes. So a controlled delivery system is necessary to deliver the drug for a prolonged time. Hence the present work was aimed to design, develop and evaluate an oral osmotic delivery system of Amlodipine Besylate using two osmogens (NaCl and KCl) in order to achieve constant and controlled release of the drug to obtain the desired therapeutic effect.

MATERIALS AND METHODS

Materials

Amlodipine Besylate was obtained from Sun Pharmaceuticals, Chennai. Ethyl cellulose, Magnesium stearate and Talc were procured from Loba Chemie Pvt. Ltd, Mumbai. Sodium chloride was purchased from Molychem, Mumbai. Potassium chloride was procured from Reachem Laboratory Chemicals Pvt. Ltd, Chennai. Polyethylene glycol 400 from Paxmy

Speciality Chemicals, Chennai, Polyvinyl pyrrolidine from Yarrow Chem. Products, Mumbai, Isopropyl Alcohol from S.D. Fine Chem. Pvt. Ltd, Mumbai and Dicalcium phosphate was procured from Finar Chemicals Ltd, Ahmedabad. All other chemicals and reagents used were of analytical grade.

METHODS

PREFORMULATION STUDIES

Compatibility Studies

To detect any interactions of drug with other excipients, the IR spectroscopic analysis was carried out. The potassium bromide disc was used for preparing sample. Pure drug and physical mixture of drug and excipients was prepared to record the spectrum in the range of 400 cm^{-1} to 4000cm^{-1} by using FTIR Spectrophotometer. If there is no change in peaks of mixtures when compared to pure drug, it indicates the absence of interactions.[8]

EVALUATION OF GRANULES

Micromeritic Properties

The Micromeritic properties of prepared granules were studied by determining various parameters like the bulk density, tapped density, angle of repose and Carr's index. The angle of repose was determined by the fixed-base cone method. Bulk and tapped density were determined using digital bulk density apparatus.[9]

PREPARATION OF OSMOTIC PUMP TABLETS

The preparation of osmotic pump tablet of Amlodipine Besylate involves two steps. They include

- Preparation of osmotic pump core tablets.
- Coating of tablets.

PREPARATION OF AMLODIPINE BESYLATE OSMOTIC PUMP CORE TABLET[10]

Four formulations of Amlodipine Besylate core tablets (F1,F2, F3 and F4) were prepared by using sodium chloride and potassium chloride as osmogens by wet granulation method. Out of which two formulations were developed by using two different osmogens separately, one formulation was in combination with two osmogens and one formulation was without osmogens (control).

PREPARATION OF POROUS OSMOTIC TABLET

Preparation of core tablets

Granules of Amlodipine Besylate were prepared by wet granulation method. All the ingredients except PVP K30, magnesium stearate and talc were accurately weighed and mixed in a mortar with a pestle for 10 minutes to get uniform mixture. The dry blend was granulated with sufficient quantity of PVP K30, which was dissolved in isopropyl alcohol. The coherent mass was kept at room temperature for air drying (until IPA smell ceases/ evaporated) and the passed through sieve No: 10. The granules were dried at 50^0C in hot air oven for two hrs. The dried granules were again passed through sieve No: 20 and once again dried in hot air oven at 50^0C for 30 minutes. The dried granules were mixed with magnesium stearate and talc and compressed into tablets using Minipress tablet punching machine. The compression was adjusted to give tablets with approximately 5-6 kg/cm^2 hardness and checked with Monsanto tablet hardness tester (Table-1).

Table 1-Formulation of Amlodipine Besylate Osmotic Pump Tablets

S.NO	Ingredients	Formulations Quantity(mg)			
		F1	F2	F3	F4
1.	Amlodipine Besylate	5	5	5	5
2.	Sodium Chloride	50	-	50	-
3.	Potassium Chloride	-	50	50	-
4.	Polyvinyl Pyrrolidine K_{30}	20	20	20	20
5.	Isopropyl Alcohol	q.s	q.s	q.s	q.s
6.	Dicalcium Phosphate	209	209	159	259
7.	Magnesium Stearate	6	6	6	6
8.	Talc	10	10	10	10
Weight of each tablet= 300 mg					

COATING OF THE CORE TABLETS

Preparation of Coating Solution[10]

As per the method described by Sakthikumar et al coating solution was prepared by mixing 5% Ethyl cellulose coating agent /semi permeable membrane and15% PEG 400 (pore former and plasticizer) with respect to ethyl cellulose were dissolved in acetone: methanol solvent(40:10) mixture and stirred to get homogeneous solution.

Dip Coating Method[11]

In the present study, dip coating method was used to coat the tablets. The weighed core tablets were dipped into the coating solutions by holding with forceps and after dipping the

coated tablets were placed on a glass plate for drying in air for 15 minutes at room temperature. The tablets were then dried at 60^0C in an oven for 30 minutes and then weighed.

EVALUATION OF OSMOTIC PUMP TABLETS

Hardness or Crushing Strength[12]

Hardness of the tablets is determined by Monsanto hardness tester, which consists of a barrel with a compressible spring. The pointer moving along the gauge in the barrel at which the tablet breaks.

Thickness

The thickness of the tablet was measured by using Vernier Caliper scale.

Uniformity of Weight or Weight variation test[13]

Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight. If the weights not more than two of the tablets differ from the average weight by more than the percentage listed in the accompanying table and no tablet differ from the average weight by more than double that percentage.

Table 2-Standard Table for Accepted limits of Weight variation

Average weight of tablet (mg)	Percentage difference
130 or less	10
More than130 and upto 324	7.5
More than 324	5

Friability[14]

Friability is a tablet property that evaluates the ability of the tablet to withstand abrasion in packaging, handling, and shipping. Friability was measured by Roche Friabilator. 20 tablets are weighed and placed in the plastic chamber. The chamber is rorated for 100 revolutions. During each revolution, the tablet falls from a distance of 6 inch. The tablets are removed from the chamber after 100 revolutions and weighed. The tablet that loses less than 1.0% of their weight are generally acceptable.

Percentage weight gain[15]

Twenty tablets (before and after coating) from each formulation were selected randomly, weighed individually and average weight was calculated. The average weight increase due to coating was determined from the difference in weight of coated and uncoated tablets.

Percentage Weight gain= (Weight gain/ initial weight before coating) x100.

Drug content analysis

Three tablets were taken and powdered. From the powder, accurately weighed amount equivalent to 100mg of Amlodipine besylate was weighed and dissolved in pH 1.2 buffer solution. The solution was suitably diluted (10µg/ml) and assayed for the drug content by measuring the absorbance at 237nm using UV-Visible spectrophotometer.

***In Vitro* Drug Release Studies[15]**

In vitro drug release of the formulations was carried out in a USP dissolution apparatus (paddle type) at a rotating speed of 50 rpm and temperature of $37^0 \pm 2^oC$. The dissolution medium was 900 ml of pH 1.2 buffer solution. Samples of 5ml were withdrawn at specified time intervals over 10-hour period and finally at 24 hour and the medium was replenished with fresh 5 ml dissolution fluid so that the volume of dissolution medium was maintained at 900ml. The withdrawn sample was transferred to 10ml standard flask, the volume was adjusted to 10ml with pH 1.2 buffer solution and analyzed spectrophotometrically at 237nm, and the drug release was calculated.

Curve Fitting Analysis/ Kinetic Studies[16]

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows.

Log cumulative percent drug release versus time (zero order kinetic model).

Log cumulative percent drug remaining versus time (first order kinetic model).

Cumulative percent drug release versus square root of time (Higuchi model).

Log cumulative percent drug release versus log time (korsmeyers Peppas model).

RESULTS AND DISCUSSION

The FTIR studies of Pure Amlodipine Besylate and Amlodipine Besylate with other excipients were carried out to study the interaction between the drug and other ingredients used. Osmogens such as sodium chloride, potassium chloride are transparent to infrared radiation. Therefore, no signals appeared for sodium chloride and potassium chloride. The major functional groups of Amlodipine Besylate in FTIR spectrum are amino group (at 3298.28),aromatic CH group(at 3030.25), aliphatic CH group(at 2985.52), ketone group(at 1685.79),carbonyl group(at1612.49), methane group(at 1205.51) appeared in the above peaks and wave number. The same functional groups are also present in the peaks and patterns of Amlodipine Besylate with other excipients. The result proved that there were no significant interactions between the drug and other excipients used in the formulations.

EVALUATION OF GRANULES

The physical characters of granules of all formulations were evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner ratio. The results are presented in Table- 3.The result showed that the angle of repose of all the formulation was between 27.69^0 and 33.20^0. It proved that the flow properties of all formulations are good. The bulk density was found in the range of 0.53-0.63g/mL. The tapped density was between 0.62-0.77 gm/mL. Both are within the acceptable limits. If the compressibility index of the powder is between 1 -20, it shows good flow characters. Here all the formulations exist in the range between 11.87 -13.52. It indicates that the granules showed good flow property. The result showed that the Hausner ratio of all the formulations was between 1.06-1.17. If the Hausner ratio lies between 1.12- 1.18, it shows good flow behaviour of the granules or powder. The result indicates good flow property of the granules.

Table 3- Evaluation of Amlodipine Besylate Granules

S. No	Parameters	Physical Characteristics of Amlodipine Besylate*			
		F1	F2	F3	F4
1	ANGLE OF REPOSE(ɵ)	$28^0.33'$±0.02	$33^0.20'$±0.04	$31^0.14'$±0.06	$27^0.69'$±0.09
2	BULK DENSITY(gm/mL)	0.61±0.01	0.627±0.04	0.625±0.01	0.53±0.01
3	TAPPED DENSITY(gm/mL)	0.62±0.01	0.769±0.01	0.71±0.01	0.67±0.02
4	COMPRESSIBILITY INDEX (%)	12.5±0.14	13.40±0.56	11.87±0.08	13.52±0.07
5	HAUSNER'S RATIO	1.06±0.07	1.13±0.01	1.12±0.14	1.17±0.04

***All values are expressed as mean±standard deviation, n=3**

EVALUATION OF OSMOTIC PUMP TABLETS OF AMLODIPINE BESYLATE

Hardness and Friability

The hardness of the coated tablets was 6.2-6.5kg/cm^2 when compared to uncoated tablets whose hardness ranges from 5.4-5.6kg/ $cm^{2.}$. Acceptable limits for both coated and uncoated oral tablets 5-8Kg/cm^2.The increase in the hardness may be due to increased coating thickness (Table-4).The friability of formulated tablets was ranging between 0.33and 0.98%. The weight loss should not be more than 1% is the accepted limit. The result showed that it was within the accepted limit (Table- 4).

Table 4- Hardness and Friability

Formulation	Hardness (kg/cm$^{2)*}$		Friability (%)*
	Uncoated	Coated	Uncoated
F1	5.5±0.47	6.4±0.16	0.33±0.20
F2	5.6±0.24	6.5±0.043	0.66±0.07
F3	5.4±0.14	6.4±0.21	0.33±0.26
F4	5.5±0.32	6.2±0.57	0.98±0.17

***All values are expressed as mean ± standard deviation, n=3**

Thickness

The thickness of the coated tablets was ranging between 2.16 and 2.22 mm whereas the thickness of uncoated tablets was ranged between 0.40 and 0.44mm. The thickness of coating was 1.76-1.79mm. The results were shown in Table 5.

Table 5- Thickness

Formulation	Thickness (mm)*		
	Uncoated	Coated	Coating membrane
F1	0.44±0.04	2.22±0.02	1.78±0.04
F2	0.42±0.07	2.21±0.05	1.79±0.02
F3	0.40±0.02	2.16±0.06	1.76±0.05
F4	0.41±0.05	2.19±0.04	1.78±0.07

***All values are expressed as mean ± standard deviation, n=3**

Weight Variation and Percentage of weight gain

The weight of one tablet 300mg. The acceptable deviation is ±10%. The result of weight variation test showed that the weight of all formulated uncoated tablets was within the range of 293.49-299.54 mg and the coated tablet was 311.38-318.28mg. The deviation of weight variation was within the acceptable limit±10%. So all the formulations passed the weight variation test (Table -6).

The percentage of weight gain after coating was found to be between 5.94-7.11%.This may be desirable to withstand the hydrostatic pressure created by the osmogens. The percentage weight gain should not be more than 8%. The result proved that the percentage weight gain was within the acceptable limit (Table-6).

Table 6- Weight variation

Formulation	Weight variation(mg)		Weight gain(mg)	Percentage weight gain (%)
	Uncoated	Coated		
F1	299.54±0.17.	318.28±0.17	18.74±0.34	6.25
F2	296.72±0.19	317.84±0.27	21.12±0.21	7.11
F3	295.41±0.32	312.98±0.42	17.57±0.74	5.94
F4	293.49±0.44	311.38±.0.17	17.89±0.45	6.00

***All values are expressed as mean ± standard deviation, n=3**

Drug content estimation

The drug content in the coated as well as uncoated tablets was found to be within the prescribed limits (±10%w/w of Amlodipine Besylate). The drug content of the coated tablet was 95.82-98.24% and uncoated tablet was 95.94 to 98.13% (Table- 7). It showed that the drug was uniformly distributed in all the formulations.

Table7- Drug Content Analysis

Formulation	Percentage of Drug Content*	
	Uncoated	Coated
F1	97.57±0.64	97.62±0.91
F2	98.13±0.17	98.24±0.14
F3	96.47±0.21	96.38±0.29
F4	95.94±0.52	95.82±0.34

***All values are expressed as mean ± standard deviation, n=3**

IN VITRO DISSOLUTION RATE STUDIES

The dissolution studies of all the coated formulations of Amlodipine Besylate were performed and the drug release was compared with conventional marketed sample of Amlodipine Besylate tablet, uncoated compressed tablet of Amlodipine Besylate and also formulation without osmogens (F4).

The percentage of drug release from the marketed product of Amlodipine Besylate tablets was 89.8% in 90 minutes whereas the drug release from the uncoated Amlodipine Besylate tablets (with osmogens) was 72.0%(F1),68.8%(F2),97.8%(F3) and 64.8%(F4- without osmogens) respectively. This increased in drug release from F3 may be due to increased in concentration of osmogens(combinations of NaCl and KCl) which produce increase in osmotic pressure and increase in number of pores on the surface of the tablet. When osmotic pressure is increased, the core compartment imbibes the aqueous fluid from the surrounding media and so the drug release was also increased. Moreover, when the number of pores

increased on the tablet surface, drug was diffused, and increased the drug release. The comparative drug release profiles were presented in Fig-1.

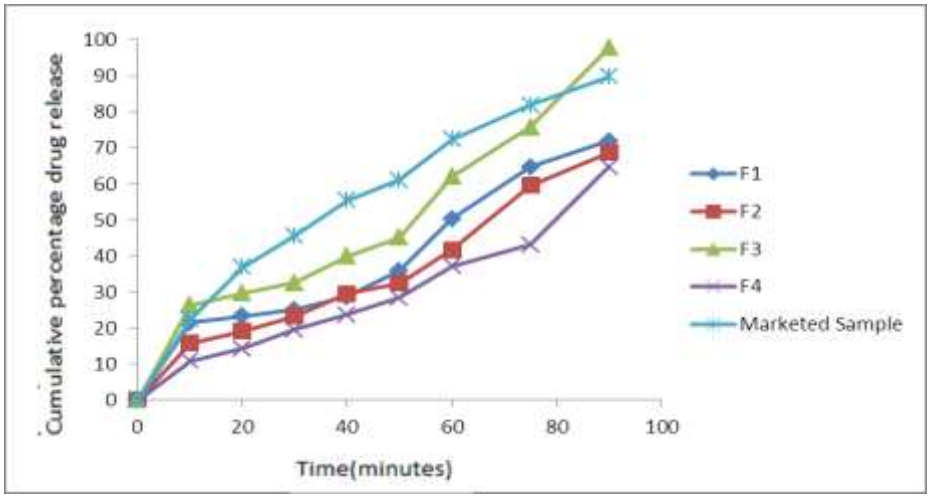

Fig 1- Cumulative Percentage of Drug Release from Uncoated and Marketed Sample of Amlodipine Besylate Formulation

Core tablets were coated with Ethyl cellulose coating solutions. The cumulative percentage of drug release from formulations F1, F2, F3, and F4 (control- without osmogen) were found to 92.6%, 87.5%, 82.4% and 89.5% respectively in 24 hours. The slow drug release compared to uncoated formulations may be due to increase in coating thickness. The results are shown in Table -8.

Table 8-Percentage Drug Release of Amlodipine Besylate Coated Osmotic Pump Tablets

S.No	Time (h)	Cumulative Percentage Drug Release (%)			
		F_1	F_2	F_3	
1	0.5	32.4±0.02	14.7±0.04	18.5±0.07	18.0±0.01
2	1	36.0±0.04	18.2±0.02	27.2±0.04	32.6±0.04
3	2	50.4±0.13	36.7±0.03	36.6±0.02	48.5±0.13
4	3	58.2±0.01	51.2±0.15	39.3±0.05	54.1±0.70
5	4	62.3±0.06	57.9±0.03	43.4±0.06	58.9±0.72
6	5	68.7±0.03	61.6±0.13	52.9±0.01	64.6±0.03
7	6	77.1±0.05	66.7±0.05	59.7±0.03	70.5±0.05
8	7	81.4±0.07	73.2±0.76	64.2±0.72	77.3±0.01
9	8	86.5±0.02	78.6±0.08	71.7±0.01	81.6±0.13
10	24	92.6±0.03	87.5±0.72	82.4±0.13	89.5±0.15

*** All values are expressed as mean ±standard deviation, n=3**

Kinetic studies

In order to understand the mechanism of drug release from all the formulations, percentage of drug release data were treated to various kinetic models like zeroorder[129], first order[138], Higuchi's model[131] and korsmeyers equation .The result showed that all the formulations were fitted to zero order kinetics which is evident from highest regression coefficient values(R^2). This confirms that the drug release from all the formulations was found to be zero order.

CONCLUSION

Amlodipine Besylate is a potent Anti-hypertensive drug and therefore a constant and controlled release of this drug is essential in curing hypertension. The above results revealed that Amlodipine Besylate formulated as elementary osmotic pump tablets provide a control release of drug upto 24 hours. Hence it can be concluded that formulation like an osmotic tablets on this drug may be considered as a suitable alternative to currently available formulations of Amlodipine Besylate.

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