WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 5, 1542-1560. Research Article ISSN 2277– 7105

FORMULATION AND EVALUTION OF SUSTAINED RELEASED MATRIX PELLETS OF DILTIAZEM HCL BY: EXTRUSION AND SPHERONIZATION

Giram P.S. and Bare A.R* and Puranik P.K.

Goverment. College of Pharmacy Aurangabad, 431005(M.S.) India.

Article Received on
07 March 2015,

Revised on 30 March 2015,
Accepted on 22 April 2015

***Correspondence for Author**
Bare A.R
Goverment.College of Pharmacy Aurangabad, 431005(M.S.) India.

ABSTRACT

Aim of this study is to prepare matrix pellets of antihypertensive drug [Diltiazem HCl]by extrusion –spheronization technique,and formulating the sustained release pellets without coating by using hydrophobic and hydrophilic matrix forming polymer like Ethylcellulose and HPMC K15M Drug -polymer interaction was studied by FTIR and confirmed by DSC. Different preliminary batches were performed and among that polymers in the ratio 3:1EC:HPMC K15 M batch pellets have good morphological properties and desire drug release. A 3^2 factorial design was used to determine the effects of the dependent and independent variables.It was concluded that significant effects were exerted not only by the operational parameters, but also by the nature of the wetting agent (liquid),binder conc. and effect of plasticizer. Friability,Content uniformity determined and in vitro drug release characteristics was studied as per USP XXIV monograph and surface morphology and particle size analysis was done by photomicroscopy. Selction and optimization was carried by using design expert 8.07.1 software.and kinetics of drug release determined by pcp v3 disso software.

KEYWORD: pelletization,extrusion spheronization, Ethylcellulose, HPMCK15M, Diltiazem HCl as model drug.

INTRODUCTION

Oral sustained release system gaining more importance in the market due to its maximium therapeutic efficiency and patient compliance.oral sustained release system is classified as reservoir,monolithic,matrix type sysem.[1] Oral delivery is frequently impaired by several physiological.Pharmaceutical challenges that are associated with the inherent

physicochemical nature of the drugs and/or the variability in GI conditions,such as pH,presence of food,transit times,expression of P Glycoprotein (P-Gp) and CYP3A,as well as enzymatic activity in the alimentary canal.[2,3] Study and Manipulation of these problems and challenges is considered an important strategy for improving or developing oral drug delivery.

Multiparticulate drug delivery system

The concept of multiple unit dosage form was initially introduced in the early 1950s. As the name implies, this type of dosage unit comprises more than one discrete unit. These forms can be defined as oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. The multiple unit dosage forms include micro granules/ spheroids, pellets, microcapsules.[4]

Pellets: Pellets for pharmaceutical applications are defined as small, spherical, free-flowing granules with a narrow size distribution, typically varying in diameter between 500 and 1500 μm, in which the active pharmaceutical ingredient (API) is present as a number of small independent subunits.To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet. Pellet disperse freely in the G.I.T. maximize drug absorption; minimize local irritation of mucosa by certain irritant drugs. Reduce variations in gastric emptying rates, flexibility in dosage form design, ease to coating these are advantages of pellet over tablet.[5] Extrusion-Spheronization technique is most advance technique of pelletization. The process of extrusion spheronization include Dry mixing: The materials was dry mixed to achieve homogeneous powder dispersion. Wet granulation**:** With the help of a suitable granulating fluid powder mixture was transformed into a sufficiently plastic wet mass. Extrusion**:** The wet mass obtained was extruded to produce rod-shaped particles of uniform diameter that was charged into a spheronizer.Spheronization**:**The extrudates were rounded off into spherical particles using a spheronizer.Drying and Screening**:** The spherical particles were then dried to achieve the desired moisture content and optionally screened to achieve a targeted size distribution.[6,7] Not all moistened powder mixtures can be successfully extruded. Newton defined the specific requirements for a wetted mass to be suitable for extrusion and spheronization[8] For successful extrusion and spheronization, microcrystalline cellulose (MCC) is incorporated in most formulations.[9] Ethylcellulose was hydrophobic matrix forming polymer show drug release retardation. HPMC K15 M was hydrohilic matrix forming polymer and swelling

agent. During dissolution, the HPMC pellets absorbed water producing a viscous gel matrix which controlled the drug release and dissolved or eroded.[10,11] TEC was used as plastciizer literature study revealed that as the plastcizer affecting drug release and surface of pellet.[12,13] The binder or wetting agent mainly affecting pellets shape,braking hardness, proper extrudates. processing parameter like spheronization speed and time needed to optimized.

Diltiazem HCl is calcium channel blocker used in the treatment of hypertension, angina pectoris and cardiac arrhythmias.Its biological half life is 3 - 4.5 hr, which is relatively short and patients are advised to take Diltiazem HCl in divided daily doses, once in every 6 to 8 hrs.[14,15] Such frequent drug administration may lead to fluctuations of blood levels,hence there is need of formulating the SR pellets which are more advantageous than tablet. The objective of this study to formulate matrix pellets without coating which releases the drug in continuously over a period of 12 hrs.

MATERIAL

Diltiazem HCl a calcium channel blocker drug obtained as gift sample from wockhardt, Aurangabad,India,Ethylcellulose [10cps] and HPMC K15M,other HPMC Grades obtained as gift sample from colorcon ,goa,India.plasticizer like triethyl citrate(TEC),obtained from IPECA,India Microcrystalline cellulose PH101 obtained as gift sample from signetchem,mumbai,and distilled water**.**

METHODS

A)Drug Identification and Drug-Excipients compatibility study

1)Melting Point: Melting point of Diltiazem HCl was determined by taking a small amount of sample in a capillary tube closed at one end and placed in Digital melting point apparatus. (Veego Digital Melting point apparatus) The melting point was recorded.

2)UV Spectrum and Calibration curve of Diltiazem HCl

Method validation of Diltiazem HCl by UV Method was carried out . The standard solutions of DLT HCl were prepared in the concentration range of 4 to 20 µg/ml by diluting stock solution (100 µg/ml) with distilled water .Its Calibration curve was take placed,lamda max was found to be 236 nm and analytical validation was determined. Drug having high solubility and high permibilty i.e.BCS Class I Drug.

3)Fourier transform infra-red spectra (FTIR)

The drug sample was placed in FTIR cuvette. The drug sample was scanned over the range of 4000-400 cm^{-1} on an FTIR (Prestige 21 SHIMADZU). The FTIR spectra of drug sample were recorded. {Drug,and mixture of drug and polymers (1:1).

4) Differential Scanning Calorimetry (DSC)

The thermal behaviour of Diltiazem HCl was studied using Shimadzu DSC TA60 WS Thermal Analyzer. Accurately weighed samples of (For drug 6.06 mg) were hermetically sealed in aluminium pan and heated at a constant rate of 20°C/min over temperature range of 100 to 300°C. The DSC thermogram was recorded. The physical mixtures of drug with polymers for compatibility studies were prepared by triturating drug and drug and polymers (1:1) in a dried mortar for 5 min and kept as it is for 24 hrs.

B)Preparation of pellets[19-20]

1) **selection of binder**

Binders are adhesive materials that are incorporated to bind powders and maintain pellet integrity. They are an essential component of pellet formulation. In all cases binders are used in concentration range of 2-5%. Some of the binder likes solution of HPMC, polyvinyl pyrolidone , hydroxy propyl cellulose etc.

Pellets without drug (dummy pellets) were prepared with various binder solutions such as water, PVP K30, HPMC (K4M, K15M, and K100M) solution in water. The responses of consistency of extrudates were studied and pellets were observed for their appearance and strength as shown in table(2).

Binder solution of HPMC K15M in water was prepared in concentration range of 2-4%w/w. Response was checked for consistency of damp mass and ability to form proper extrudates and good pellets. The effect of binder concentration was improper extrude (if 2%),good extrude(3%) and at 4%conc.it gives sticky extrudates.Hence used the HPMC K15 M as binder solution(3%w/w).it gives good integrity, excellent shape pellets . similarly conc. Of plasticizer TEC was optimized(2%).

2)Preparation of binder gel

Weighed accurately HPMC K 15 M powder and slowely poured into distilled water having temp.70-90c ,then continuously stirred using machanical stirrer untill no lump remain .To

prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20–30% of the required amount of water. The water should be vigorously stirred and heated to 80–90C, then the remaining hypromellose should be added. Sufficient cold water should then be added to produce the required volume.[22]

3)Preparation of Different Concentration % (TEC) Plasticizer Solution

Different Concentration [1%, 2%, 3% v/w] TEC were prepared by adding 0.5, 1, and 1.5 ml of TEC in 50gm HPMC K15M (3%) binder solution respectively. Subsequently solutions were kept for stirring using mechanical stirrer to give homogenous solution of plasticizer. For preliminary study 2% TEC solution in 3% HPMC K15M) was used as optimized concentration.

4)Optimization of Extrusion Spheronization Process

As the literature reveal that spheronization speed and time of spheronization affecting the pellets shape, roundness,and pellet size hence to optimized speed and time,formulating the dummy pellets batches at three different speed and time Thus, 32 =9 formulations were prepared.

Speed of spheronization (X1) = 1300, 1500, 1700 rpm
Time of spheronization (X2) = 10, 15, 20 min.

5)Formulation of pellets

Powder of all the ingredients are passed through sieve no.40 separately ,then weighed accurately ,Mixing of all weighed ingredients was performed by using geometric and bag shaking method,.Addition of binder solution in optimized concentration and water as q.s. that lead to formation of dump mass having enough moisture.Amount of water added was also affecting the extrudiblity of wet mass and indirectly process.[21] The wet mass was kneaded Then wet mass passed through extruder and extrudes formed that transfer to spheronization at optimizied speed and time.

The formula content 20% drug loading The drug release rate retarding polymer EC and HPMC K15M was used in the ratio3:1 respcetively, the optimized binder conc. was 3%w/w and 2% TEC as plastcizer.

The wet mass obtained was extruded by roller extruder. Extrudate was then spheronized using a Spheronizer; equipped with cross hatched plate 4.2 mm at 1500 rpm for 20 min.

(Extruder 20 and Spheronizer 250, Anish Pharma, India) the optimized process variable as shown in table(1).The time and speed of the spheronization were determined by the experimental design.The pellets were dried under the same conditions, at 40 ± 2^0C and sieve through 40#screen.

Factorial design

A 3^2 factorial design was applied to optimize the concentration of two different polymer to observe the combine effect of polymer on the drug release pattern for getting the sustained release of Diltiazem HCl the factors included were the quantity of EC(A) and, HPMC K15M(B) values as shown in table(3) at constant speed and time. The approximate levels of these independent variables were chosen from drug release profile of preliminary batches**.**The factorial batches in coded terms and actual composition of factorial batches was shown in table(3)&(4)respectively.

It is assumed that the independent variables affect response in linear, quadratic and cubic manner. This assumption is necessary to develop a mathematical model which can be tested for significance of contribution of various independent variables. Hence, it becomes essential to use a factorial design with 3 levels to estimate curvature in response (i.e.3^2 factorial with total no. of experiments = 9). To save time, single block design with zero (0) replication has been preferred. The experimental grid was coded for ease of representation in Table no.3.

Design expert 8.0.7.1 software was used for statistical analysis, During the mathematical evaluations, the confidence interval was 95%, i.e. the differences were significant if $p < 0.05$.

C)Evaluation of pellets

1).Flow property of pellets: All the factorial batches are evaluated for angle of repose, bulk density, tapped density, carr's index, and hausner ratio. as literature revealed that angle of repose is ≤25 then flow is excellent, and Hausner ratio is in the range 1-1.10 then flow is excellent.[23]

2) Morphological study: All the factorial batches were studied for morphological features like roundness, aspect ratio, pellet size, and shape by using optical microscopy (Olympus® CX31 equipped with Magnus® pro v.3.0 software) . Depending on the results obtained from this analysis, optimized batch having aspect ratio nearer to 1 and maximum roundness was selected.

3) Friability: 2gm accurately weighed pellets were taken from each batch of the pellets and placed in a friabilator and tumbled for 100 revolutions at 25 rpm. Twelve steel balls (weighing 0.445g each) were used as an attrition agent. After friability testing, the pellets were sieved through sieve no 22. The weight loss after friability testing was calculated as.[24]

$$friablity = \frac{w0 - w1}{w1} \times 100$$

Where, W0= initial weight of pellets and W1 = final weight of pellets

Upper acceptability limit of friablity was 0.8-1%.

4) Drug content

Accurately weighed 450 mg of pellets(equivalent to 90mg drug) were crushed in dried mortar pestle. Powder of pellets was dissolved in 100 ml of distilled water. Sample was stirred for 15 min and filtered. Standard dilution of the sample was prepared and analyzed by UV-spectrophotometer at 236.0 nm.

5) *In vitro* drug release study

Dissolution studies were conducted in USP Type-I dissolution apparatus(Lab india) using 900 ml of distilled water as dissolution medium the basket was rotated at a speed of 100 rpm and the temperature was maintained at 37±0.5°C This operation was continued for 12 hours. At every 1-hour interval samples of 5 ml were withdrawn from the dissolution medium and replaced with fresh dissolution medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed at 236 nm for Diltizem HCl by UV spectrophotometer (Shimadzu, Japan). The amounts of drug present in the samples were calculated with the help of straight-line equation obtained from the calibration curves for respective drug.[25,26]

F) Kinetics analysis of drug release

To analyze the mechanism of drug release from the pellets the *In vitro* dissolution data were fitted to zero order, first order, Higuchi release model, Hixson and Crowell powder dissolution method and Korsmeyer Peppas model by using PCP Disso Version 3 software, and the model with the higher correlation coefficient was considered to be the best model. Korsmeyer. Derived a simple relationship which described drug release from a polymeric system equation.

$$Mt / M\infty = Ktn$$

where Mt / M∞ is a fraction of drug released at time t, k is the release rate constant and n is the release exponent. The n value is used to characterize different release for cylindrical shaped matrices. In this model, the value of *n* characterizes the release mechanism of drug as described in Table 1.For the case of cylindrical tablets, 0.45 ≤ n corresponds to a Fickian diffusion mechanism, 0.45 < n <0.89 to non-Fickian transport, n = 0.89 to Case II(relaxational) transport, and n > 0.89 to super case II transport.[27,28]

E) Statistical analysis by Design Expert Software

A 3^2 full factorial design was selected and the 2 factors were evaluated at 3 levels, respectively. Ethylcellulose (X1), HPMC K15M (X2) were selected as independent variables and the dependent variables were % Drug release at 12 hrs(Q_{12}), aspect ratio, Roundness The data obtained were treated using Design Expert 8.0.7.1 software and analyzed statistically using analysis of variance (ANOVA) .The data were also subjected to 3-D response surface methodology to study the interaction of Ethylcellulose (X1), HPMC K15M (X2) on dependent variables.

RESULTS AND DISCUSSION

A) Drug Identification and drug-excipients compatibility study

1) Melting Point

The melting point of Diltiazem HCl was determined on Digital melting point apparatus was found to be 212º-215ºC which is in good agreement with reported melting point.

2) UV Spectrum and Calibration curve of Diltiazem HCl

The UV spectrum of Venlafaxine HCl solution (10µg/ml) exhibited wavelength of absorbance maximum at 236 nm which complies with the reported and calibration curve shows r^2=0.999.

3) Fourier transform infra red spectrophotometer (FTIR)

Drug-polymer interaction or compatibility study was carried out by FTIR and confirmed by DSC thermogramm as shown in figure.(2). FTIR indicated the absence of any interaction between drug and excipients used in the preparation, as there was no considerable change in characteristic bonds for functions such as >C=O, N-H, and C-H groups.

In all physical mixtures of drug and polymer, there was neither masking of single characteristic peak nor existence of additional peak in the spectra. as seen in Fig.(2) and Table (5) so we can conclude that drug and polymers are compatible with each other.

4)DSC

The possibility of interaction between Diltiazem HCl, and their excipients were also studied by DSC. When Diltiazem HCl was mixed with EC and HPMC K 15M endothermic peak was obtained at 215°C which complied with that of pure drug. Similarly, there was not considerable change in DSC peak.Hence, there was no interaction of drugs with excipients and they were compatible. DSC thermograms was shown in Figures(3).

B)Evaluation of pellets

The present work was focused on optimization of process variables, formulation and evalution of pellets prepared by extrusion spheronization. developed sustain release formulation for 12 hrs.

Flow property

Flow and mechanical property was studied, as the flow pattern shown in table (6) show that all factorial batches have the angle of repose values ranges from 10.39±0.31 to 17.18±0.30. The value of bulk density and tapped density ranges from 0.76±0.051 to 0.91±0.04 gm/cm^3 and 0.84±0.003to 1.015±0.002 gm/cm^3, respectively. Hausner's Ratio of F2,F3,F5,and F7 are in the range of 1.00-1.11 hence flow pattern of these batches was excellent.

Morphology of pellets

Morphological stdies by optical microscopy as shown in table(7) shape, aspect ratio, roundness and pellet size was determined. as batch F7 show aspect ratio 1-1.12, maximum roundness 95% and pellet size in the narrow range was 841-1022. The Photo micrographic study also confirmed that batch F7 shows pellets possessing more sphericity uniform pellets with smooth surface than that of other batches. The comparative studies of photomicrograph of all batches are shown in Figure(4).

Loss on drying,friability and drug content: The loss on drying of pellets of optimized batch was found to be 0.3% and thus pellets with less moisture content were obtained. The friability was studied in order to determine the mechanical properties of the pellets. The friability of the pellets tested with steel balls was below 0.2%, and thus the pellets have

desirable hardness and of good quality with respect to friability. The preliminary aim to produce mechanically strong pellets was there by achieved, The drug loaded pellets of Diltiazem HCl prepared with optimized formula and there exhibited drug loading capacity or content uniformity found in the rang of 89-97%.

Dissolution study*:* *In-vitro* drug release study of all formulation batches (F1-F9) were performed in triplicate using USP apparatus Type-I (Basket), 100rpm and distilled water as dissolution medium .the batch F1 and F4 shows 97.77±1.25 % and 92.80±0.76 % drug release respectively in the 9 hrs.F1 and F4 batch can not sustained the release upto 12 hrs.the other batches F2,F3,F5,F6,F7,F8,F9 are able to sustained the drug release upto 12hrs.Among these batches F2 and F7 showed the 90.7±0.55 % and 93.31±1.12% drug release at 12 hrs respectively. The Batches F2,F5&F7 shows better drug release and it was within the acceptance limit which was defined by USP32NF27.As shown in Table 8. The result of percentage of drug release (%) of all formulation batches was shown inTable(9&10) and Figure(5).

Kinetics of drug release

To describe the kinetics of the drug release from the matrix pellets, release data was evaluated by model-dependent (curve fitting) method using PCP Disso v3 software and model with the higher correlation coefficient was considered to be the best model. The results showed that the most factorial batches F1, F2, F3, F4, F5, F6, F7,followed kosmayer peppas and F8, F9 followed matrix order kinetics. The observations are summarized in Table(11). as the n value of optimized batch F7was 0.571it indicate that drug release by ficknian diffusion mechanism.

Statistical analysis

From the ANOVA study of percent drug release, aspect ratio and roundness it found that of p value for percent drug release, aspect ratio and roundness were found to be less than 0.05 indicate that model was significant, and best fit model for response surface design was quadratic model. This study carried by using design expert software.It observed that as the change in the concentration of polymer namely Ethylcellulose(A) and HPMC K15M(B),it affect the percent drug release, aspect ratio and Roundness as shown in figure(6).

Final equation in terms of coded factors for percent drug release

Q=92.58-4.03(A)-1.46(B)-3.54(AB)-3.37(A2)-1.41(B2)

Final equation in terms of coded factors for aspect ratio

Aspect ratio =1.2411-0.39833A-0.10833B+0.0575AB+0.1883A2+0.058333B2

Final equation in terms of coded factors

Roundness =92.89-8.0A-3.83B-4.5AB-8.33A2-2.83B2.

List of Abbreviations

DLT HCl	:	Diltiazem HCl
EC	:	Ethyl cellulose
HPMC	:	Hydroxy propyl methyl cellulose
MCC PH101	:	Microcrystalline cellulose
TEC	:	Triethylcitrate
conc	:	Concentration
Abs	:	Absorbance
SR	:	Sustain Released
CR	:	Controlled Released
ANOVA	:	Analysis of variance
% DR	:	Percent drug release
SD	:	Standard deviations
%RSD	:	Percent relative standard deviation
nm	:	Nanometer
µg/ml	:	Microgram per mililiter

Table 1: Optimized parameters for extrusion spheronization

Parameter	Value
Spheronization speed	1500 rpm
Spheronization time	20 min
Extrusion speed	46 rpm
Extrusion sieve	1 mm
Spheronization plate	4.2 mm

Table 2: Selection of binder

Binder solution	Concentration	Response
Water	q.s.	Failed to form continuous extrudates ,more sticky
PVP K30D	10-20 %	Extrudates were not of desired size required
HPMC K4M	2-4 %	Inconsistency in forming uniform extrudates
HPMC K15M	2-4 %	Gives good, uniform, consistent, extrudates
HPMC K100M	2-4 %	Improper extrudates due to high viscosity

Table 3: Factor combination as per experimental design.in coded terms

	Batch code								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
A	-1	-1	-1	0	0	0	1	1	1
B	-1	0	1	-1	0	1	-1	0	1

Table 4: Composition of factorial batches

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Diltiazem HCl	6	6	6	6	6	6	6	6	6
MCC101	20	18.5	17	19.5	18	16.5	19	17.5	16
Ethylcellulose	3	4.5	6	3	4.5	6	3	4.5	6
HPMC K15M	1	1	1	1.5	1.5	1.5	2	2	2
Binder solution(3%w/wHPMC K15M+2%v/w TEC)	15								
Distilled water	q.s.								

*All weigh are in gms

Table 5: functional group and their absorbance

Absorption band (cm^{-1})	**Attributed to**
2837	**Aliphatic C-H**
3342	**Aromatic C-H**
2360	**Amine HCl-NH**

Table 6: Flow property of pellets

Factorial Batches	**Flow property**				
	Angle of Repose (°)	**Bulk density (gm/cc)**	**Tapped density (gm/cc)**	**Carr's Index (%)**	**Hausner's Ratio**
F1	13.15±0.42	0.88±0.04	0.92±0.003	3.17±0.15	1.23±0.03
F2	14.54±0.28	0.89±0.02	0.94±0.004	0.315±0.40	1.05±0.01
F3	14.02±1.09	0.91±0.04	1.01±0.0021	11.3±0.28	1.10±0.06
F4	11.35±0.34	0.76±0.051	0.84±0.003	6.04±0.39	1.17±0.02
F5	12.52±0.56	0.81±0.03	0.87±0.002	4.47±0.33	1.08±0.02
F6	16.21±0.30	0.82±0.012	0.95±0.005	9.35±0.51	1.16±0.04
F7	10.39±0.31	0.90±0.04	0.96±0.004	2.9±0.48	1.06±0.01
F8	17.18±0.30	0.83±0.07	0.88±0.006	6.06±0.23	1.14±0.07
F9	15.58±0.28	0.77±0.05	0.86±0.005	3.4±0.66	1.21±0.03

Table 7: Morphological characteristics of pellets

Batches	Shape	Aspect ratio	Roundness(%)	Pellet size (mm)
F1	Spherical+oval	1.000-1.23	80-94	389-856
F2	Spherical+oval+dumbbell	1.000-1.15	76-93	406-974
F3	Oval+dumbbell	1.007-1.2	71-92	753-1115
F4	Oval+dumbbell	1.036-1.181	71-85.5	574-1072
F5	Spherical	1.006-1.219	83-92	658-937
F6	Cylindrical+Oval	1.057-1.817	60-84	722-1274
F7	Spherical	1.000-1.12	88-95	841-1022
F8	Cylindrical+Dumbell+oval	1.150-1.247	56-93	693-1366
F9	Cylindrical+Dumbell	1.000-2.900	64-83.36	726-1472

Table 8: Official Dissolution Acceptance Limit

Time (in hours)	Amount dissolved
3	Between 10%and 25%
9	Between 45%and 85 %
12	Not less than 70%

Table 9: Percent Drug Release (%) of F1 to F4

Time[Hr]	F1	F2	F3	F4
0	0	0	0	0
1	10.65±0.3	4.4±0.11	8.3±0.07	7.61±0.49
2	16.88±0.35	15.59±0.08	16.59±0.16	17.9±0.67
3	46.77±0.37	20.69±0.39	19.37±0.26	32.16±1.16
4	59.35±0.88	31.21±0.35	29.55±0.27	45.65±1.17
5	67.61±0.38	39.87±0.22	39.71±0.41	55.38±1.83
6	78.29±0.47	59.46±0.66	56.43±0.61	75.76±1.05
7	86.97±0.33	70.7±0.62	65.47±1.5	81.73±1.34
8	93.38±1.33	79.07±1.3	74.14±2.33	87.36±0.08
9	97.77±1.25	85.69±0.49	77.42±2.03	92.80±0.76
10	95.14±0.97	87.54±1.32	80.69±1.9	95.39±1.91
11	91.07±0.22	90.2±1.4	85.3±0.75	94.03±2.02
12	87.21±2.22	90.7±0.55	86.73±1.1	91.26±1.73

*All values are expressed as mean± SD, n=3.

Table 10: Percent Drug Release (%) of F5 to F9

Time [Hr]	F5	F6	F7	F8	F9
0	0	0	0	0	0
1	3.17±0.31	3.81±0.19	6.84±0.54	2.381±0.32	1.28±0.17
2	12.84±0.14	12.19±0.34	14.53±0.14	13.75±0.81	11.57±0.21
3	18.52±0.27	17.66±0.09	24.18±0.45	20.82±0.88	17.92±0.58
4	26.79±0.47	27.19±0.54	30.72±0.29	28.3±0.85	25.66±0.65
5	39.52±1.26	39.9±0.38	46.89±0.8	36.23±1.19	35.52±1.2
6	55.78±0.57	51.99±0.7	57.6±1.2	56.91±0.19	48.92±0.86

7	70.72±0.43	69.2±1.18	71.82±0.67	68.90±1.8	57.17±1.25
8	73.4±1.07	71.24±1.2	77.25±1.18	73.23±0.58	62.53±1.33
9	77.09±0.13	75.9±0.29	84.53±0.35	78.96±0.56	67.97±0.76
10	81.24±1.21	71.37±8.3	88.31±0.66	81.38±0.83	73.66±1.48
11	86.92±1.49	79.16±1.05	92.23±0.48	84.34±1.02	76.74±0.38
12	90.35±1.53	84.47±1.63	93.31±1.12	88.16±1.08	78.35±0.36

*All values are expressed as mean± SD, n=3.

Table 11: Drug release kinetics of all factorial batches

Batch Code	r^2					n	K
	Zero order	First order	Matrix	Korsmeyer peppas	Hixon crowell		
F1	0.8939	0.8940	0.9476	0.9519	0.8940	0.355	0.0126
F2	0.9835	0.9835	0.9150	0.9890	0.9835	0.472	0.0055
F3	0.9844	0.9845	0.9256	0.9898	0.9844	0.485	0.0079
F4	0.9545	0.9545	0.9435	0.9804	0.9545	0.727	0.0063
F5	0.9839	0.9839	0.9096	0.9867	0.9839	0.546	0.0042
F6	0.9784	0.9784	0.9130	0.9881	0.9784	0.692	0.0046
F7	0.9863	0.9863	0.9269	0.9893	0.9863	0.571	0.0079
F8	0.9817	0.9817	0.9125	0.9760	0.9817	0.824	0.0038
F9	0.9886	0.9886	0.9150	0.9652	0.9886	0.928	0.0026

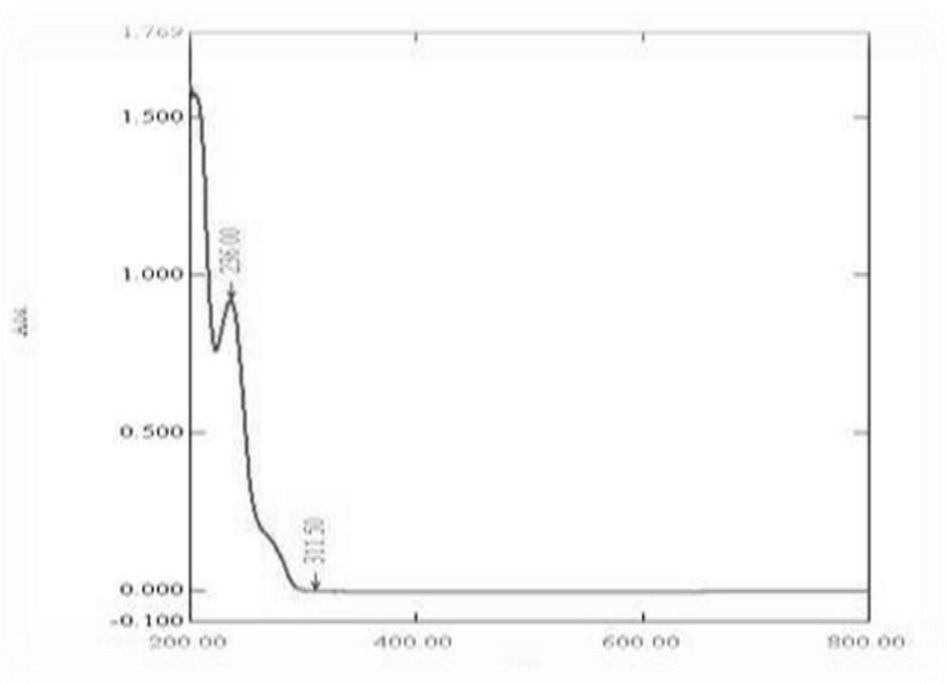

Figure 1: UV spectra of Diltiazem HCl

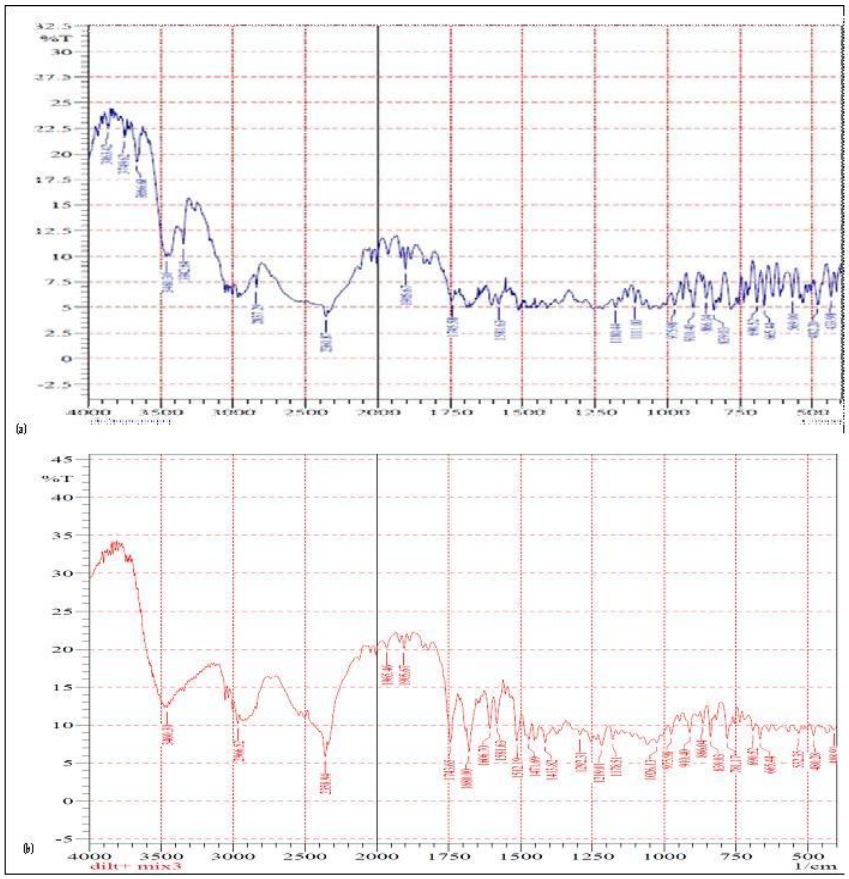

Figure 2: FTIR spectrum of (a)Diltiazem HCl (b)Diltiazem HCL+excipients

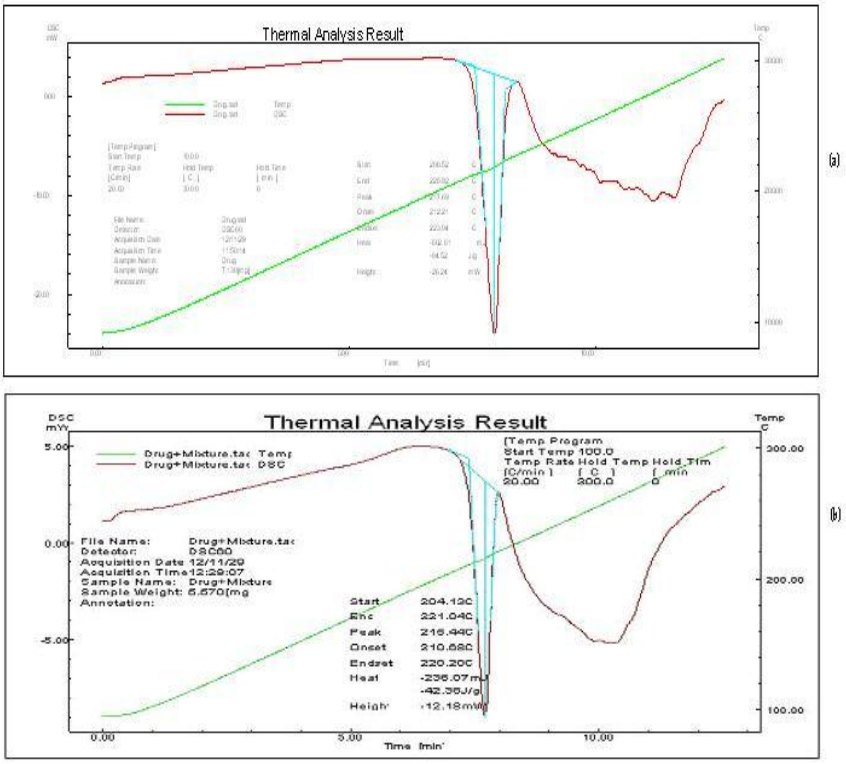

Figure 3: DSC thermogram of (a)Diltiazem HCl(b)Diltiazem HCl+excipients

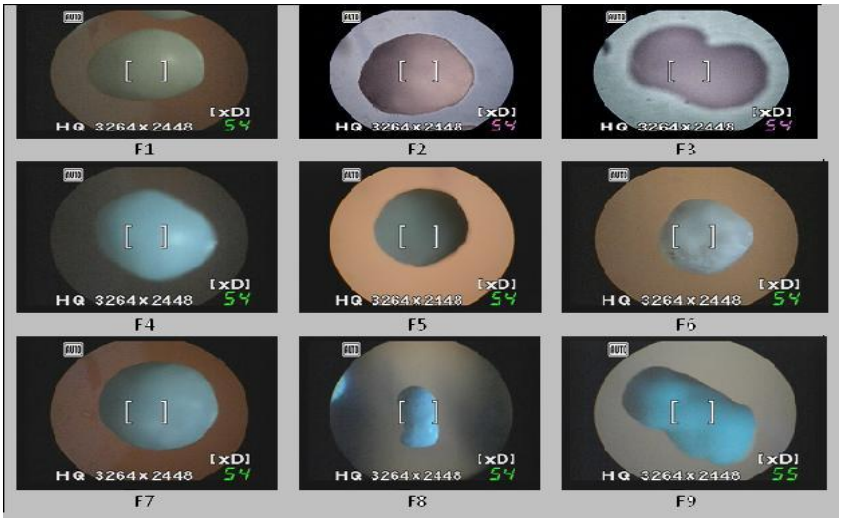

Figure 4: Photomicrographs of pellets of factorial batches (F1-F9)

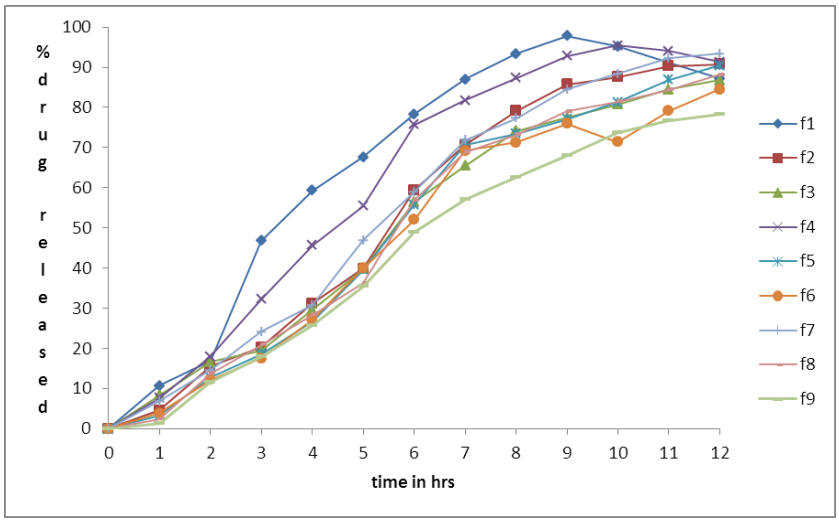

Figure 5: Graph of percent drug release

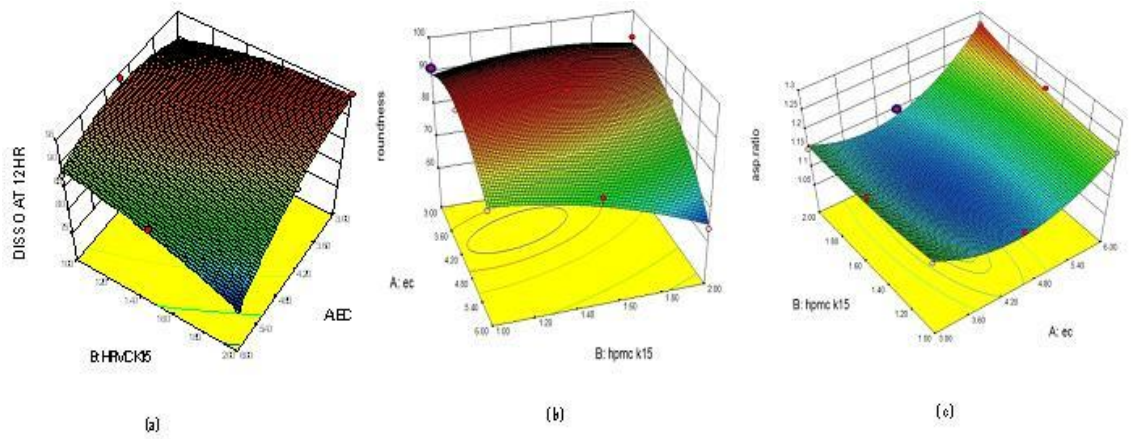

Figure 6:3D surface response plot of (a)percent drug release,(b)roundness,(c)aspect ratio.

CONCLUSION

The results of this study showed that combination of EC as hydrophobic and HPMC K15 M as hydrophilic matrix forming polymer in the ratio 3:1 and TEC(2%) as potential plasticizer is effective and useful for sustaining the Drug release to treat hypertension. The resultant optimum formulation F7 was selected from the factorial batches on the basis of sphericity, particle size, and in-vitro drug released studies it showed 92.7% drug release at 12 hrs and have within acceptance limit as per USP.This study resolved the extrusion spheronization technique as a promising approach for formulation of sustained release matrix pellets of Diltiazem HCl without coating.

ACKNOWLEDGEMENT

The authors are grateful to wockhardt pvt ltd.Auranagbad for providing the drug as gift sample We are also thankful to all the faculty of Govt. College of Pharmacy, Aurangabad for valuable guidance and support.

REFERENCES

1. Nicholas G., Sustained release dosage forms. In Lachman L., Liberman HA, editors, The theory and practice of industrial pharmacy,third edition ,Varghese Publishing House, Bombay., 2009; 455.
2. Brahmankar D.,Jaiswal S.,Biopharmaceutics and Pharmacokinetics; A Tretise. 2nd edition, Delhi:Vallabh Prakashan. 2009; 39-50.
3. Marrianne A, Factor affecting drug absorption:` GI tract physiology and drug absorption' , Aulton M. E.(eds)pharmaceutics the science of dosage form design;2nd ed; Churchill livingsone: New York, 2002; 224.
4. Collett j, Moreton c, Mutiparticle: modified release peroral dosage form. Aulton, M. E.(eds)pharmaceutics the science of dosage form design; 2nd ed.;Churchill livingsone., 2002; 289.
5. Sellasie IG., Knoch A,Pelletization techniques; In Swarbrick J, editor, Encyclopedia of pharmaceutical technology, 3rd ed., 2007; 2651.
6. Bechgaard H, Hagermann NG, Advantages of multiparticulate system, Drug Dev. Ind. Pharm., 1978; 53-67.
7. Mehta A.M, Pharmaceutical Pelletization technology, In Ghebre-Sellassie I, (Ed.) drugs and pharmaceutical sciences, Marcel Dekker Inc. New York, 1989; 241-265.

8. Newton J.M, Extrusion and Extruders, In:Swarbrick J, Boylan J.C (Eds.), Encyclopedia of Pharmaceutical Technology, Marcel Dekker Inc., New York and Basel, 2002; 1220–1236.
9. Hamedelniel E.I, Bajdik J, Pintye-Hodi K, Optimization of preparation of matrix pellets containing Ethylcellulose, Chemical Engineering and Processing., 2010; 49: 120-124.
10. Chatlapalli R, Rohera BD, Physical characterization of HPMC and HEC and investigation of their use as pelletization aids,. Int J Pharm., 1998; 161: 179-193.
11. Carmen F. R., Hydrophilic Cellulose Derivatives in Wise, D.L. Handbook of Pharmaceutical Controlled Release Technology; Marcel Dekker: New York, 2005; 1: 211, 435-440.
12. Schilling S.U,Lirola H.L, Shah N.H, Waseem Malick A.and McGinity J.W, Influence of plasticizer type and level on the properties of Eudragit S100 matrix pellets.
13. Kibria G,Monzurul AR, Effect of Plasticizer on Release Kinetics of Diclofenac Sodium Pellets Coated with Eudragit RS 30 D, AAPS Pharm Sci Tech., 2008; 9: 1240-1246.
14. Tripathi KD, Essential of medical pharmacology, Fifth ed., Jaypee brothers medical publishers ltd., 2004; 491-498.
15. Website: http//www.drugbank.ca/Diltiazem HCl july., 2011; 7.
16. Goskonda S.R, Gregory AH, Upadrashta S.M, Controlled release pellets by extrusion-spheronization, Int J Pharm., 1994; 111: 89-97.
17. Sinha V.R, Agrawal M.K, Kumria R, and Bhinge J.R, Influence of Operational Variables on Properties of Piroxicam Pellets Prepared by Extrusion-Spheronization: A Technical Note, AAPS PharmSciTech., 2007; 8(1): 20.
18. Zhang H, Luo Y.H, Zhao Z.Y,Chen Q,Luo M, Preparation of carteolol hydrochloride matrix sustained-release pellets and evaluation in vitro/in vivo African Journal of Pharmacy and Pharmacology., 2012; 829-833.
19. Pai R, Kohli K, Extended release matrix pellets: preparation and compression into disintegrating tablet, International Journal of Drug Delivery., 2011; 329-339.
20. Gandhi R, Kaul C ,Panchagnula R., Extrusion and spheronization in the development of oral controlled-release dosage forms, Elsevier Science PSTT., 1999; 2.
21. Makoto O., Jian G, Yoshihisa M,Effect of amount added water during extrusion-Spheronizer process on pharmaceutical properties of granules. Drug Dev Ind Pharm., 1994, 20(19): 2977-2992.
22. Rowe R.C, Sheskey P.J,Handbook of pharmaceutical excipients,5th ed,pharmaceutical press, 2006; 346-348.

23. Martin A, Swarbrick J,Physical pharmacy, Third ed., Varghese publishing house, Bombay, 1991; 517-519.
24. Lachman L, Lieberman H.A, Kanig J.A, The Theory and Practice of Indutrial Pharmacy, Third ed., Varghese publishing house, Bombay, 1987: 68: 88.
25. United States Pharmacopoeia 32-NF 27, United States Pharmacopoeial Convention, Rockville, 2009; 2160-2162.
26. Zahirul I. Khan, Dissolution testing for sustained or controlled release oral dosage forms and correlation with in vivo data: challenges and opportunities, Int J Pharm, 1996; 140: 131-143.
27. Costa P, Lobo J.S, Modeling and comparison of dissolution profile, Euro. J. Pharm. Sci., 2001; 12: 123-133.
28. Peppas N.A.: Int. J. Pharm., 1983; 15- 25.