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FORMULATION AND CHARACTERISATION OF SUSTAINED RELEASE CARVEDILOL TABLET FROM RESERVOIR PELLETS

Amit M. Gupta* and U. D. Shivhare

Department of Pharmaceutics, Sharad Pawar College of Pharmacy, Nagpur, Maharashtra, India

Keywords:

Sustained release tablets, Matrix tablets, Disintegrant pellets, Characterization of pellets, Reservoir pellets.

Correspondence to Author:
Amit M. Gupta

Ph.D. scholar,
Sharad Pawar College of Pharmacy, Wanadongri, Hingna road, Nagpur – 441110, Maharashtra- India.

E-mail: amitmgupta31@gmail.com

ABSTRACT: Sustained release Carvedilol tablets constituting reservoir pellets developed in this study is an attempt to investigate the effect of drug release from matrix. The sustained release Carvedilol tablets were prepared by using different combination with release modifier (ethyl cellulose 10 cps and Eudragit RS 100). Tablets containing disintegrant pellets (Crosspovidon) with active ingredient demonstrated a sustained rate of drug release. The Carvedilol tablets were prepared using different ratios of pellets. After 12 hours of dissolution study, Carvedilol release from the matrix systems were 92.35%, 92.37%, 95.25%, 93.26%, 92.87% and 90.4 2% from formulation F1, F2, F3, F4, F5 and F6 respectively. Formulation F2 (10% of Eudragit RS 100) exhibited 95.21% Carvedilol release in 12 h and satisfied all the physical evaluation parameters hence, considered as optimized batch. The Carvedilol sustained release F2 batch showed non-Fickian diffusion kinetics.

INTRODUCTION: Pellets defined as a small free flowing spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipient using appropriate processing equipment. Reservoir pellets consisting of a drug-layered as starter core and a water-insoluble polymer coating to control the release of the active compound, have become increasingly important for sustained drug delivery [1].

However, drug release is a complex interplay of the coating and the drug core. While the polymer mainly governs factors, like the permeability of a film coating and release.

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Release depending on the properties of the drug core like coating hydration, medium uptake, drug dissolution, build-up of hydrostatic pressure and potential crack formation [2].

With reservoir-type coated pellet dosage forms, the polymeric coating must be able to withstand the compression force; it can deform, but it should not rupture. Polymers used in the film coating of solid dosage forms fall in two broad groups based on either cellulosic or acrylic polymers [3].

MATERIALS: Carvedilol obtained as a gift sample from Sun Pharmaceutical industries Ltd., Vadodara, Gujarat. Crosspovidon HPMC K4M and MCC pH 101 and all other chemicals and reagent were of analytical grade.

RESULT:

Preparation pellets: The sustained release matrix tablets were formulated by using drug, disintegrant

and coating material like ethyl cellulose and Eudragit RS 100. The non-pareil seeds were loaded with Carvedilol suggested as in step I referred as drug pellets. The step I referred as drug pellets prepared by loading the Carvedilol on non-pareil seeds, in the step II disintegrant Crosspovidon layered on non-pareil seed referred as disintegrant pellets. Finally, the Carvedilol loaded pellets of step I layered with several coats of ethyl cellulose or Eudragit RS 100 referred as soft pellets (III step). By using various ratio of these pellets sustained release tablet were prepared and evaluated for further investigation to obtain best formulation, which obeys the maximum characteristics to fulfil the desired requirements [4, 5, 6, 7].

TABLE 1: FORMULA FOR PREPARING CARVEDILOL UNCOATED PELLETS

Ingredients	FC 1
Carvedilol B.P.	12.5 mg
HPMC K4M	2.5 mg (20%)
MCC pH 101	3.750 mg (30%)
Magnesium stearate	0.250 mg (2%)
PEG 400	0.125 mg (1%)
Talc	0.375mg (3%)
Ethanol	q.s

TABLE 2: FORMULA FOR PREPARING DISINTEGRANT PELLETS USING CROSSPOVIDON

Ingredients	FP1	FP2	FP3
Crosspovidon	5%	5 %	5 %
HPMC K4M	20%	30%	40%
MCC pH 101	30%	30%	30%
Magnesium stearate	2%	2%	2%
PEG 400	1%	1%	1%
Talc	3%	3%	3%
Ethanol	q.s	q.s	q.s

TABLE 3: FORMULA FOR CARVEDILOL COATED PELLETS USING ETHYL CELLULOSE AND EUDRAGIT RS100

Ingredients	FAC 1	FAC 2	FAC 3	FAC 4	FAE 5	FAE 6	FAE 7	FAE 8
Carvedilol	Carvedilol uncoated pellets FC1							
Ethyl cellulose	5%	7%	10%	15%	----	----	----	----
Eudragit RS100	----	----	----	----	5%	07%	10%	15%
PEG 400	1%	1%	1%	1%	1%	1%	1%	1%
Ethanol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Evaluation of Pellets prepared in step I, II and III:

Size distribution/Sieving method:

50 gm of sample weighted and placed on top sieve of mechanical sieve shaker and shake for 20 min. After removing, the sieves pellets retained on each sieve weighed. These processes were following for all the formulated pellets [8, 9, 10]. The percentage weight of powder retained on each sieve calculated using following formulas given in equation 01 and 02:

Weight size = Mean size of sieve opening **x** %

Weight retained on smaller sieve..... (01)

Particle size= weight size / 100..... (02)

TABLE 4: SIEVE ANALYSIS FOR PELLETS

Pellets	Sieve Number	Mean size Opening (micron) (3)	Weight retain (over size)	% Weight retain (over size) (5)	Weight size 3× 5
Carvedilol	Sieve 40/60	337.5	6.75	13.50	4556.25
	Sieve60/ 80	215	7.20	14.40	3096.00
	Sieve 80/100	165	23.43	46.86	7731.90
	Fine	125	12.62	25.24	3155.00
Crosspovidon	Sieve 40/60	337.5	6.85	13.70	4623.75

disintegrant	Sieve 60/ 80	215	9.25	18.50	3977.50
pellets	Sieve 80/100	165	19.06	38.12	6289.80
	Fine	125	14.84	29.68	3710.00
Carvedilol	Sieve 40/60	337.5	6.55	13.10	4421.25
ethyl cellulose	Sieve 60/ 80	215	9.25	18.50	3977.50
coated	Sieve 80/100	165	19.90	46.80	7722.00
pellets	Fine	125	12.20	21.60	2700.00
Carvedilol	Sieve 40/60	337.5	8.02	16.04	5413.50
Eudragit	Sieve 60/ 80	215	9.10	18.20	3913.00
RS 100	Sieve 80/100	165	22.58	45.16	7451.40
coated pellets	Fine	125	10.30	20.60	2575.00

Particle size = weight size /100

The particle size analysis of different types of pellets; drug pellets (Carvedilol), soft pellets coated with ethyl cellulose 10 cps and Eudragit RS 100 and disintegrant pellets through sieve analysis from the sieve shaker. The particles pass through #60 and retain on #100 i.e. particle ranging 150-350 micron are used for further investigation.

The regular size of pellets does not interact in tablet compression without damaging the tablet core hence the drug release could be maintain for longer time. The mechanical properties of drug pellets, coated pellets and disintegrant can affects the reservoir pellets and it has equal importance in drug release mechanism of sustained release.

Physical evaluation of pellets [11, 12]:

Intragranular porosity:

The intragranular porosity of the pellets was calculated (n=1-3) as one minus the ratio of the effective and apparent particle densities. The effective pellet density determined by mercury pycnometer.

Bulk density:

Accurately weighed quantities of the pellets added to the cylinder with the aid of a funnel. Typically, the initial volume was noted and the sample was then tapped until no further reduction in volume was noted. The volumes before and after tapping were used on the standard equation to compute bulk and tapped density respectively.

Compressibility index:

The compressibility index and the closely related Hausner's ratio have become the simple fast and popular methods of predicting powder flow characteristics. The compressibility index has been propose as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of materials. Both are determined by measuring both the bulk volume and tapped volume of a powder. The basic procedure is to measure the unsettled apparent volume and the final tapped volume of the powder after tapping the material until no further volume changes occur. The compressibility index and the Hausner's ratio calculated as follows:

$$\text{Compressibility index} = \frac{100 \times \text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \quad \ldots\ldots\ldots\ldots (03)$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \ldots\ldots\ldots\ldots\ldots\ldots (04)$$

Angle of repose:

The angle of repose determined by funnel method. The accurately weighed powder blend taken in a funnel. The height of the funnel adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder blend. The blends allowed to flow freely onto the surface. The diameter of the powder cone measured and angle of repose calculated using the following equation:

$$\tan \theta = h/r \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (05)$$

Where, h and r are the height and radius of the powder cone respectively.

The results of physical evaluation of all the different pellets were described in the **Table 5**

TABLE 5: PHYSICAL EVALUATION FOR UNCOATED PELLETS

Pellets	Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index	Hausner's ratio	Angle of repose
Carvedilol	FC1	0.566 (±0.026)	0.629 (±0.023)	10.01 (±0.033)	1.111 (±0.027)	24.82 (±0.042)
Crosspovidon disintegrant pellets	FP1	0.445 (±0.092)	0.550 (±0.028)	19.09 (±0.017)	1.235 (±0.073)	22.15 (±0.033)
	FP2	0.462 (±0.044)	0.562 (±0.075)	17.79 (±0.063)	1.216 (±0.039)	24.74 (±0.013)
	FP3	0.465 (±0.013)	0.573 (±0.088)	18.84 (±0.028)	1.232 (±0.055)	24.21 (±0.022)
Carvedilol ethyl cellulose coated pellets	FAC1	0.525 (±0.032)	0.649 (±0.087)	19.10 (±0.029)	1.236 (±0.048)	23.35 (±0.014)
	FAC2	0.557 (±0.081)	0.672 (±0.062)	17.11 (±0.036)	1.206 (±0.021)	22.98 (±0.034)
	FAC3	0.559 (±0.049)	0.679 (±0.095)	17.67 (±0.021)	1.214 (±0.077)	24.56 (±0.078)
	FAC4	0.571 (±0.061)	0.682 (±0.046)	16.27 (±0.056)	1.194 (±0.072)	26.34 (±0.027)
Carvedilol Eudragit RS 100 coated pellets	FAE1	0.487 (±0.033)	0.562 (±0.011)	13.34 (±0.022)	1.154 (±0.067)	25.35 (±0.078)
	FAE2	0.490 (±0.088)	0.578 (±0.053)	15.22 (±0.073)	1.179 (±0.072)	22.64 (±0.012)
	FAE3	0.475 (±0.094)	0.565 (±0.069)	15.92 (±0.038)	1.189 (±0.059)	25.56 (±0.082)
	FAE4	0.458 (±0.071)	0.555 (±0.081)	17.47 (±0.024)	1.211 (±0.083)	26.33 (±0.074)

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

The physical evaluation performed for the consolidation and compression properties for individual pellets of Carvedilol. These evaluations include bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose. The results are satisfactory and within the prescribe range indicates good flow ability and compressibility.

Scanning electron microscopy for appearance [15, 16, 17, 18, 19]:

Microphotographs obtained from pellets loaded with Carvedilol using a scanning electron microscope (SEM). Surface structure studies carried out at SAIFFT, Cochin at various magnifications [13, 14, 15].

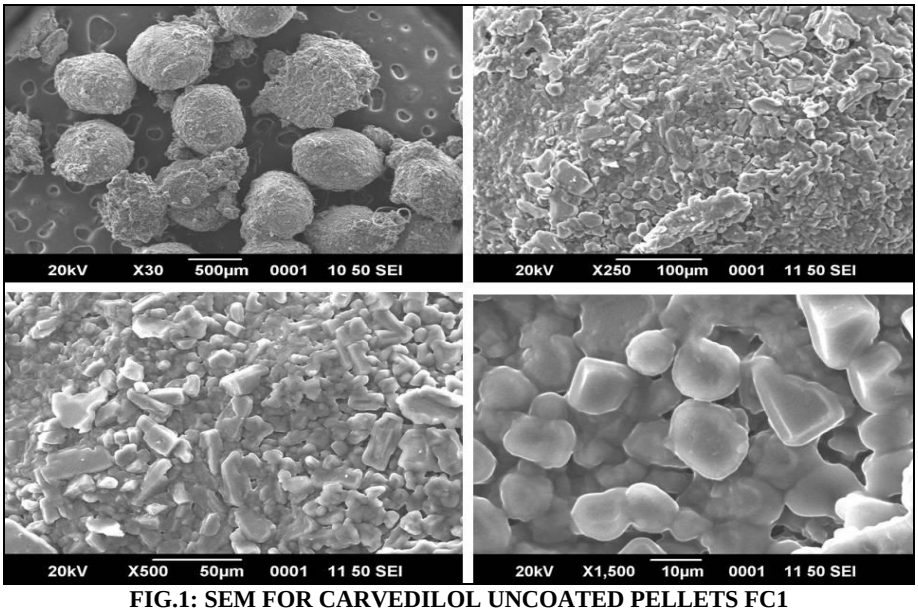

FIG.1: SEM FOR CARVEDILOL UNCOATED PELLETS FC1

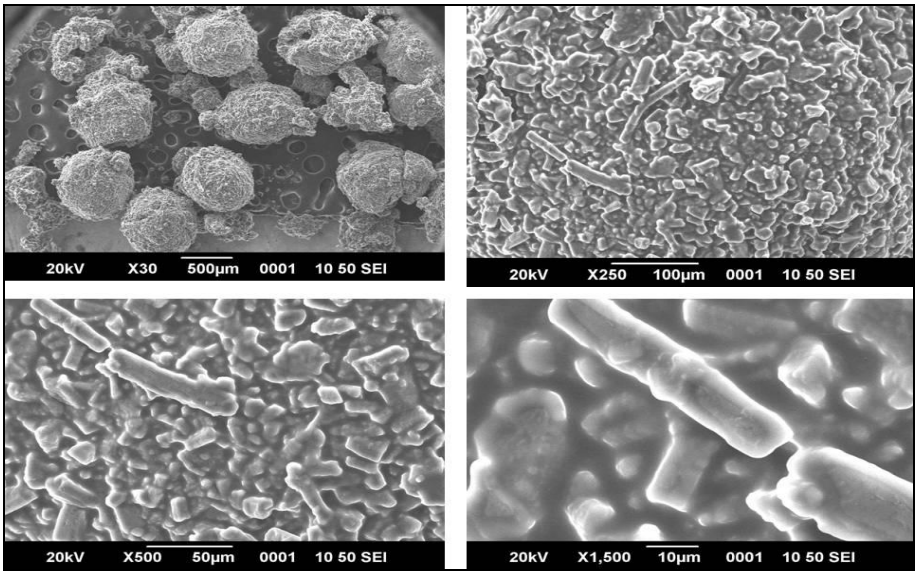

FIG. 2: SEM FOR OPTIMIZED CARVEDILOL COATED PELLETS

Visually the **Fig. 1** and **2** shows similar appearance and indicates no change in physical parameters. The surface of Carvedilol pellet was smooth as observed in SEM micrographs. The difference between surface roughness parameter were statistically and significant. Such difference could explain in terms of the particle size of the active ingredients.

Formulation of sustained release tablets from reservoir pellets:

The final tablets were prepared by using different ratio of pellets formulated in step I, II and III considered as drug, disintegrant and soft respectively. By using various ratios of pellet and excipients sustained release tablets prepared. The various trail batches of different ratio of pellets evaluated [16, 17]. Optimized batch was examined for further investigation and evaluation as drug-excipient interaction studies i.e. FTIR, flow properties (such as bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose), weight variation, thickness, hardness and friability, *in-vitro* release studies (dissolution test) and analysis of dissolution data using Kinetic models.

Drug-polymer interaction study:

The drug-polymer interaction study carried out using Fourier transform infrared spectroscopy (FTIR). The IR spectrum of pure drugs Carvedilol (A), optimized formulation (B), Eudragit RS100 (C) and Crosspovidon (D) were recorded in the stretching frequency range 400-4000 cm^{-1}. Studies carried at Sophisticated Test & Instrumentation Centre, Cochin University of Science and Technology, Cochin using KBr pellet technique [18,19, 20, 21, 22]. Graphs of FTIR studies have shown in **Fig. 3**.

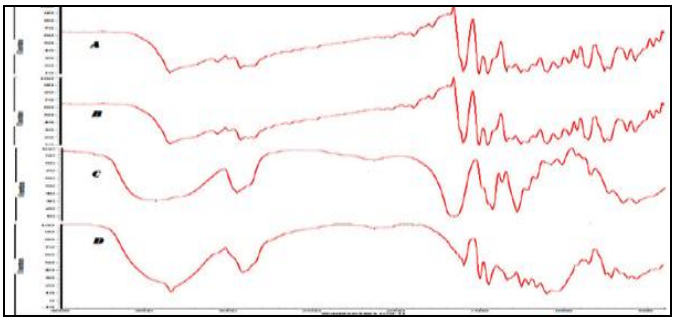

FIG. 3: DRUG-POLYMER INTERACTION STUDY FOR CARVEDILOL

The IR spectrum of Carvedilol (**Fig. 3**) shows medium absorption bands at 3344.07 and 3343.13 cm^{-1} which assigned to the drug –NH symmetric and asymmetric stretching vibrations, respectively. The other characteristic bands may attribute to the following group vibrations: 2924.34 and 2913.56 cm^{-1} (C–H stretch, respectively), 1501.76 and 1500.90 cm^{-1} (C–C stretch [in–ring], respectively), 1093.73 and 1163.83 cm^{-1} (C–H wag [–CH2X], respectively). The other bands attribute 3063.15 cm^{-1} (O–H stretch), 2130.90 cm^{-1} (C≡N stretch) and 1337.41 cm^{-1} N–O symmetric stretch nitro compounds.

From the graphs of FITR results shows that, there is no appreciable change in the positions of the

characteristic bands, compare with the formulation's IR spectrum. Since there is no change in the nature and position of the bands in the formulation, it concluded that the drug maintains its identity without going any chemical interaction with the polymers used.

Evaluation of tablets for post compression properties:

The post compression study includes thickness, hardness, friability, weight variation and assay are found in the range specified [23, 24, 25]; the data are tabularized in **Table 6**.

TABLE 6: EVALUATION OF OPTIMIZED TABLETS FOR COMPRESSION PROPERTIES

Formulation code	Average thickness (mm)	Average hardness (kg /cm2)	Friability (%)	Percentage weight variation	Assay (%)
F 1	3.62(±0.024)	6.32(±0.062)	0.19(±0.056)	4.15(±0.032)	99.42
F 2	3.46(±0.048)	6.15(±0.056)	0.27(±0.038)	3.92(±0.054)	99.76
F 3	3.56(±0.037)	6.45(±0.011)	0.42(±0.022)	3.87(±0.089)	98.12
F 4	3.58(±0.094)	6.31(±0.023)	0.16(±0.034)	4.21(±0.013)	99.78
F 5	3.64(±0.016)	6.34(±0.032)	0.13(±0.076)	3.78(±0.037)	102.21
F 6	3.56(±0.45)	6.51(±0.041)	0.27(±0.016)	4.03(±0.047)	101.67

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

The Carvedilol trial 56 (F2) gives average thickness 3.46 mm, average hardness 6.15 kg/cm^2, friability 0.27%, percentage weight variation 3.92 and assay 99.76%. The Carbamazepine trial (F2) gives average thickness 4.95 mm, average hardness 5.52 kg/cm^2, friability 0.36%, percentage weight variation 3.63 and assay 101.41%. The results of post compression study are finding in the range specified in Pharmacopeia.

TABLE 7: CUMULATIVE *IN-VITRO* DRUG RELEASE STUDY FOR TRIAL BATCHES OF CARVEDILOL F1TO F6

Sr. No.	Time (h)	pH of medium	Percentage drug release F1	Percentage drug release F2	Percentage drug release F3	Percentage drug release F4	Percentage drug release F5	Percentage drug release F6
1	1	1.2	15.27	14.21	14.29	14.22	11.22	14.01
2	2	1.2	29.34	25.75	27.44	28.28	23.67	24.56
3	3	7.2	40.68	42.54	44.56	44.43	38.66	40.92
4	6	7.2	54.76	60.56	62.71	62.43	58.42	62.44
5	8	7.2	76.34	76.43	73.59	77.4	69.71	72.78
6	10	7.2	87.69	85.75	88.32	84.36	80.25	86.04
7	12	7.2	94.36	95.21	94.67	92.34	92.69	94.35

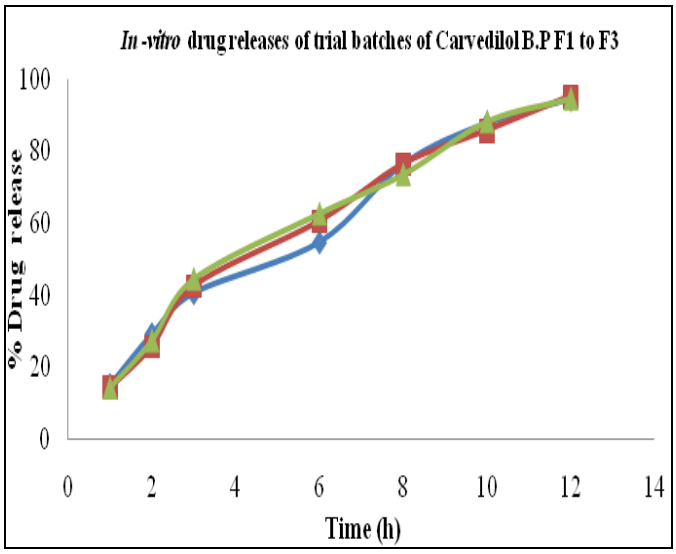

FIG.4: *IN -VITRO* DRUG RELEASES OF TRIAL BATCHES OF CARVEDILOL F1 TO F3

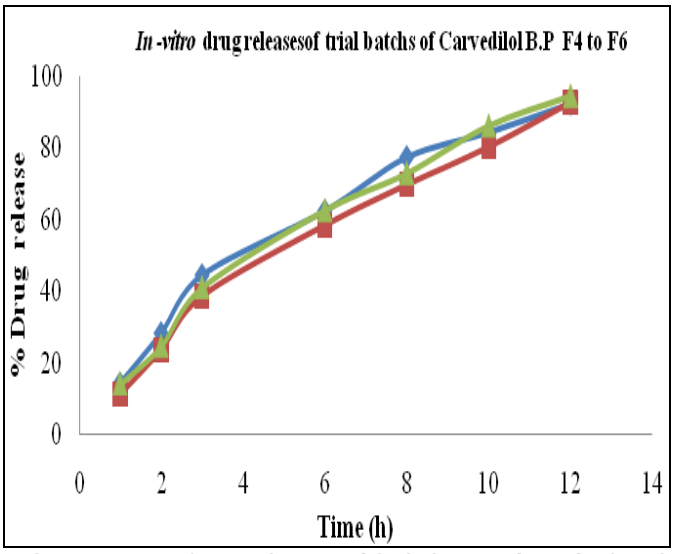

FIG.5: *IN -VITRO* DRUG RELEASES OF TRIAL BATCHES OF CARVEDILOL F4 TO F6

From the findings of the dissolution analysis data interpreted as F2 batch of Carvedilol shows 95.21% means 11.90 mg Carvedilol release in 12 h. Hence, from dissolution analysis and physical evaluation results F2 considered as optimized batches as the results were within the prescribed limits. This batches used for further investigate as optimized batches.

Stability analysis for optimized batches:

The stability study of the Carvedilol tablet (F2) was carried out according to ICH guidelines at 40 ± 2^{O}C and 75 ± 5% relative humidity for three months by storing the samples in stability chamber [26, 27, 28, 29]. The result of stability analysis of Carvedilol for physical analysis was described in **Table 8** whiles the results of *in-vitro* analysis in **Table 9** and **Fig. 6**

TABLE 8: PHYSICAL STABILITY ANALYSIS OF CARVEDILOL F2 BATCH

Sr. No	Evaluation Test	Initial	End of 1st month	End of 2 nd month	End of 3 rd month
1.	Thickness (mm)	3.46(±0.048)	3.42(±0.033)	3.48(±0.021)	3.41(±0.017)
2.	Hardness (kg /Cm^2)	6.15(±0.056)	6.12(±0.011)	6.14(±0.037)	6.18(±0.086)
3.	Friability (%)	0.27(±0.038)	0.32(±0.054)	0.23(±0.041)	0.35(±0.077)
4.	Percentage weight variation	3.92(±0.054)	3.35(±0.022)	3.76(±0.048)	3.12(±0.087)
5.	Assay (%)	99.76	99.62	99.72	99.67

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

TABLE 9: *IN-VITRO* DRUG RELEASE STUDY FOR STABILITY OF CARVEDILOL F2 BATCH

Sr. No.	Time (h)	pH of medium	Amount of drug released	Percentage drug release
1	1	1.2	1.532	12.26
2	2	1.2	3.276	26.21
3	3	7.2	5.461	43.69
4	6	7.2	7.817	62.54
5	8	7.2	9.486	75.89
6	10	7.2	10.790	84.32
7	12	7.2	11.782	94.26

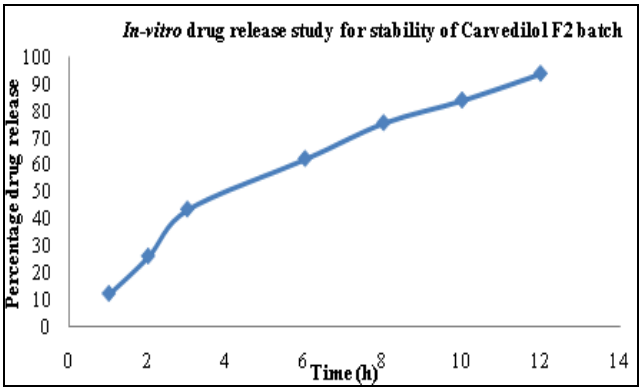

FIG.6: *IN-VITRO* DRUG RELEASE STUDY FOR STABILITY OF CARVEDILOL F2 BATCH

TABLE 10: KINETIC ANALYSIS FOR THE F2 OPTIMISED BATCH OF CARVEDILOL TABLETS

Model Fitting	R^2	T-test	k	Interpretation
Zero order	0.9571	8.087	1.0649	Passes
1st order	0.9636	8.831	-0.0112	Passes
Matrix	0.9842	13.637	3.1333	Passes
Korsmeyer-Peppas	0.9912	18.346	1.9817	Passes
Hixsen-crowell	0.9615	8.571	-0.0037	Passes
Best fitted model: Korsmeyer-Peppas				
Parameters for Korsmeyer-Peppas Equation				
n =			0.7300	
k =			1.9817	

The results of stability study for optimized Carvedilol F2 interprets that after the three months the physical evaluation and *in-vitro* drug release data were satisfactory and within the prescribed range.

Kinetics of drug release:

Different kinetic models (zero-order, first-order, matrix, Korsmeyer's -Peppas and Hixsen-crowell equation) were applied to interpret the release profile (the order and mechanism of drugs release) from sustained release system [30, 31].

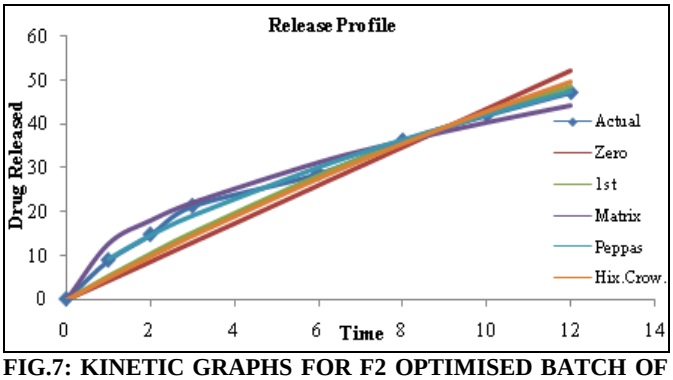

FIG.7: KINETIC GRAPHS FOR F2 OPTIMISED BATCH OF CARVEDILOL TABLETS

The results show that regression coefficient value closer to unity in the case of the zero order plots indicates that the drug release follows a zero order mechanism. The results also internet that lesser linearity in graphs of first order but at the same time Korsmeyer-Peppas Equation fitted in all the dissolution data kinetic. Here the value of the exponent "n" which is obtained from the slope of the graph of log Q (amount of drug dissolved) Vs log t (time) yielded the values. From the reference values, of exponent n in the range of $0.7300<n<1$ is indicative of anomalous transport or non - Fickian diffusion.

DISCUSSION AND CONCLUSION: The major aim of this work was to identify the major parameters affecting drug release from matrix-coated pellets. Geometry of the drug type, drug loading, additive, polymer type, core and coat type, size, release from tablets, stability and kinetics has investigated. Varying the type of the polymer had a great impact on release. Carvedilol release (F2 batch show 95.21%) was much faster from Eudragit RS 100 than from ethyl cellulose coating and this had attributed to the higher polymer permeability of Eudragit RS 100. The drug release was show drug partition into the polymer and hence that release have related with permeability of the matrix. This work shows the importance of some key factors to consider when designing coated sustained release formulation using reservoir pellets and provides deeper information about the appropriate storage conditions to guarantee an optimized finished product.

Way to design oral modified release systems is to coat pellets with a polymer that regulates drug release rate, such reservoirs pellets can be compacted into sustained release tablets. The tablets normally intended to disintegrate into discrete pellets in the gastrointestinal tract and the drug should subsequently release in a controlled manner from the individual pellets.

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