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Preparation and Evaluation of Sustained Release Carbamazepine Tablet from Reservoir Pellets.

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ABSTRACT

The present works enlighten the effect of drug release from matrix tablet in sustained manner using reservoir pellets. The Carbamazepine sustained release tablets were prepared by using different combination of reservoir pellets coated with ethyl cellulose 10 cps and Eudragit RS 100. The Carbamazepine tablet prepared using different ratio of pellets and investigates for physicochemical properties. After 12 hours of dissolution study, Carbamazepine 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 F3 exhibited maximum percentage release in 12 hours hence considered as optimized batch and all the tablet formulations showed desirable physical properties. At the same time Carbamazepine sustained release F3 batch showed non-Fickian diffusion kinetics.

Keywords: Sustained release tablets, Matrix tablets, Characterization of pellets, Reservoir pellets, Carbamazepine tablet

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INTRODUCTION

Sustained drug delivery systems to their therapeutic benefits include maximized coverage and minimized fluctuation in plasma concentrations, especially for drugs with a narrow therapeutic index, reduction in dosing frequency, improved efficacy and reduced adverse events, increased convenience and patient compliance, more uniform effect and reduction in gastro-intestinal irritation and other dose-related side effects. [Qiu Y et al., 2009].

Pellets defined as geometrical agglomerates obtained from diverse starting materials (sucrose, starch, microcrystalline cellulose, etc) and can be produced by different process conditions. Pellets loaded with different drugs can be blended and formulated in a single dosage form. This allows the administration of two or more types of drugs that may or not be chemically compatible, at the same or different sites within the gastro-intestinal tract. [Pearnchob N et al 2002] In order to achieve controlled drug release, pellets can be directly coated with a polymer: drug solution or dispersion (matrix coated pellets) or loaded with drug by a layering technique and further coated with a polymeric solution or dispersion (reservoir coated pellets) described in Figure 1. [Bodmeier R et al., 1997]

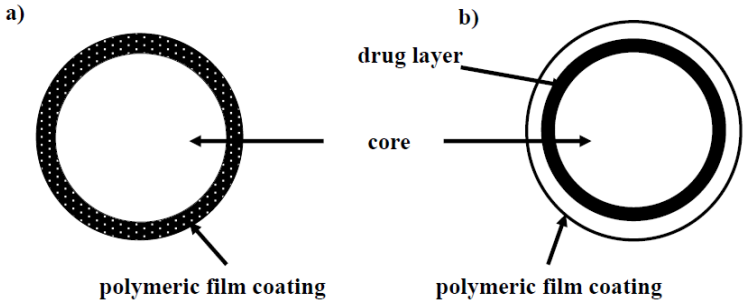

Figure 1: Schematic presentation of, a) matrix coated pellet and b) reservoir coated pellet

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. 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. 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. [Gandhi A and Kumar H, 2014] 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. [Nithiyananthan TS et al., 2009]

Materials

Carbamazepine 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.

EXPERIMENT AND RESULT

Preparation pellets [Srujan R et al., 2011][Podczeck F et al., 2008][Guanhao Y et al., 2007][Nantharat P and Roland B, 2003][Nasim SA et al., 2012]

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 Carbamazepine suggested as in step I referred as drug pellets. In step II, the disintegrant Crosspovidon layered on non-pareil seed referred as disintegrant pellets. In step III, the drug loaded pellets of step I, layered with several coats of ethyl cellulose and Eudragit RS 100 referred as soft pellets. All pellets prepared (Table 1-3) by three different steps were subject to physical evaluation.

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Table 1: Formula for preparing Carbamazepine uncoated pellets

Ingredients	FD 1
Carbamazepine	200 mg
HPMC K4M	40 mg (20 %)
MCC pH 101	60 mg (30 %)
Magnesium stearate	4 mg (2 %)
PEG 400	2 mg (1 %)
Talc	6 mg (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 Carbamazepine 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
Carbamazepine	Carbamazepine uncoated pellets FD1							
Ethyl cellulose	5 %	5 %	5 %	5 %	5 %	5 %	5 %	5 %
Eudragit RS100	----	----	----	----	----	----	----	----
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 [Costa FO et al., 2004][Fasiuddin AM et al., 2012][Sreekhar C and Christy MW, 2008][Siva PG and Mohini K, 2012][Mutalik S et al., 2007][Raymond CR et al., 2005]

Size distribution/Sieving method [Ankarao V et al., 2012]

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
Carbamazepine	Sieve 40/60	337.5	8.20	16.40	5535.00
	Sieve60/ 80	215	9.45	18.90	4063.50
	Sieve 80/100	165	22.07	44.14	7283.10
	Fine	125	10.28	20.56	2570.00
Crosspovidon disintegrant pellets	Sieve 40/60	337.5	6.85	13.70	4623.75
	Sieve 60/ 80	215	9.25	18.50	3977.50
	Sieve 80/100	165	19.06	38.12	6289.80
	Fine	125	14.84	29.68	3710.00
Carbamazepine ethyl cellulose coated pellets	Sieve 40/60	337.5	7.85	15.70	5298.75
	Sieve 60/ 80	215	8.92	17.84	3835.60
	Sieve 80/100	165	20.95	41.90	6913.50
	Fine	125	12.28	24.56	3070.00
Carbamazepine Eudragit RS 100 coated pellets	Sieve 40/60	337.5	7.25	14.50	4893.75
	Sieve 60/ 80	215	8.29	16.58	3564.70
	Sieve 80/100	165	19.96	39.92	6586.80
	Fine	125	14.50	29.00	3625.00

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. 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)

Particle size = weight size /100

The particle size analysis of different types of pellets; drug pellets (Carbamazepine), 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 [Fini A et al., 2008][Erica F et al.,2005][Gonul N et al., 2000]

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:

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

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

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:

$$\tan \theta = h/r \quad \text{.....(05)}$$

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
Carbamazepine	FD1	0.510 (±0.078)	0.588 (±0.087)	13.26 (±0.071)	1.152 (±0.086)	23.36 (±0.046)
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)
Carbamazepine ethyl cellulose coated pellets	FAC1	0.487 (±0.021)	0.592 (±0.066)	17.73 (±0.093)	1.210 (±0.042)	22.56 (±0.012)
	FAC2	0.495 (±0.017)	0.605 (±0.034)	18.18 (±0.045)	1.220 (±0.038)	24.25 (±0.034)
	FAC3	0.477 (±0.029)	0.582 (±0.045)	18.04 (±0.023)	1.221 (±0.049)	22.87 (±0.042)
	FAC4	0.514 (±0.096)	0.609 (±0.062)	15.59 (±0.077)	1.184 (±0.041)	25.67 (±0.027)
Carbamazepine Eudragit RS 100 coated pellets	FAE1	0.514 (±0.042)	0.609 (±0.064)	15.59 (±0.087)	1.180 (±0.049)	23.56 (±0.091)
	FAE2	0.519 (±0.038)	0.617 (±0.047)	15.88 (±0.035)	1.188 (±0.033)	25.24 (±0.011)
	FAE3	0.536 (±0.090)	0.612 (±0.062)	12.41 (±0.076)	1.141 (±0.020)	23.57 (±0.062)
	FAE4	0.533 (±0.032)	0.605 (±0.077)	11.90 (±0.043)	1.135 (±0.016)	24.69 (±0.024)

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

The physical evaluation performed for the consolidation and compression properties for individual pellets of Carbamazepine. 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 flowability and compressibility.

Scanning electron microscopy for appearance [Balagani PK et al., 2013][He W et al., 2008][Pachuau L et al., 2013][Kadam VD and Gattani SG, 2009][Pongjanyakul T et al., 2004]

Microphotographs obtained from pellets loaded with Carbamazepine using a scanning electron microscope (SEM). Surface structure studies carried out at SAIFFT, Cochin at various magnifications.

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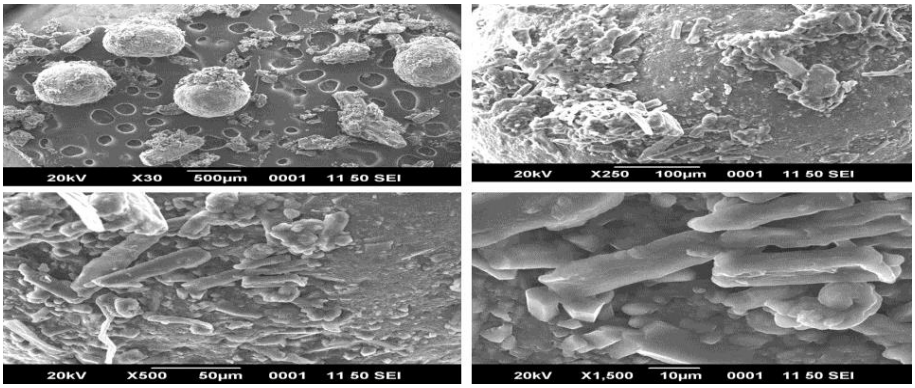

Figure 2: SEM for Carbamazepine uncoated pellets FD1

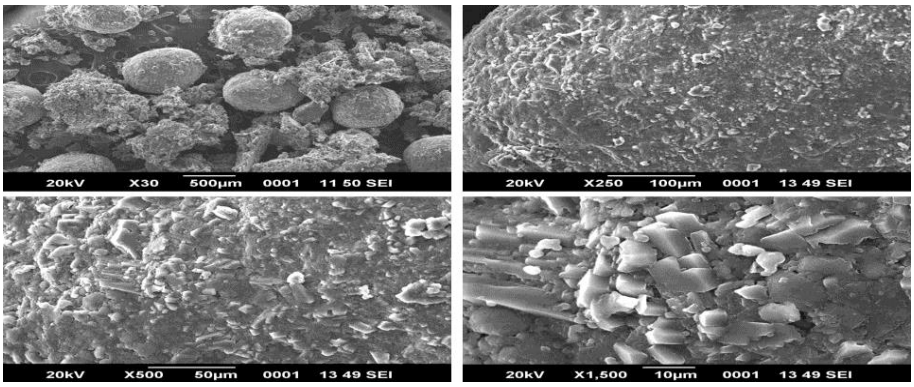

Figure 3: SEM for optimized Carbamazepine coated pellets

Visually the Figure 2 and 3 shows similar appearance and indicates no change in physical parameters. The surface of Carbamazepine 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 [Hindustan AA et al., 2010][Jaber E et al., 2008][Lalduhsanga P et al., 2013]

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. 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 [Ashok RC and Priya RV, 2008][Pintu KD et al., 2011][Gowda DV et al., 2010][Varma MM and Razia Begaum SK, 2012]

The drug-polymer interaction study carried out using Fourier transform infrared spectroscopy (FTIR). The IR spectrum of pure drugs Carbamazepine (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. Graphs of FTIR studies have shown in Figure 4.

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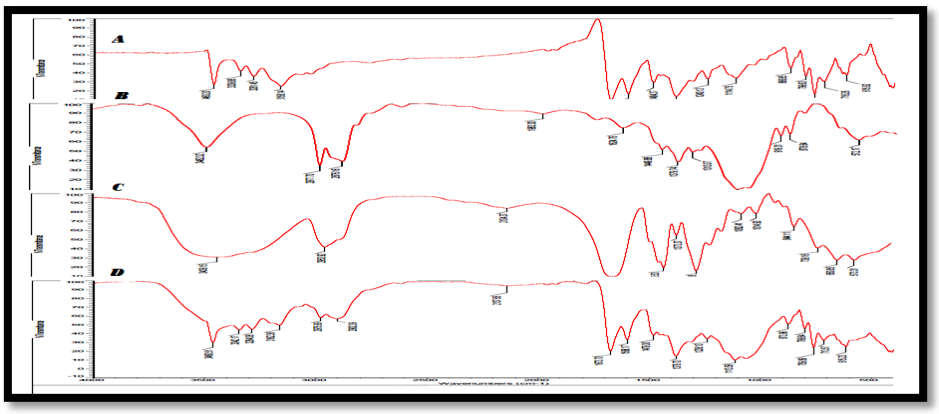

Figure 4: Drug-polymer interaction study for Carbamazepine

The IR spectrum of Carbamazepine (Figure 4) shows medium absorption bands at 3339.88 and 3342.17cm^{-1} which assigned to the drug –NH symmetric and asymmetric stretching vibrations, respectively. The other characteristic bands may attribute to the following group vibrations: 3460.20 and 3460.51 cm^{-1} (O–H stretch, H–bonded, respectively), 1674.89 and 1673.70 cm^{-1} (C=O stretch or unsaturated aldehydes or ketones, respectively), 1484.37 and 1479 cm^{-1} (N–O asymmetric stretch, respectively), 866.85 and 873.96 cm^{-1} (=C–H bends, respectively). Similarly, at 799.63 and 799.84 cm^{-1} (N–H wag 1^{O}, 2^{O} amines, respectively) and –C≡C–H: C–H bend at 615.92and 615.23 cm^{-1} respectively. The other bands attribute 2902.39 cm^{-1} (=C–H stretch) and 2137.65 cm^{-1} (-C≡C stretch).

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 [Phutane P et al., 2010][Reddy AM et al., 2013][Kaza R et al., 2009][Raghavndra NG et al., 2009]

The post compression study includes thickness, hardness, friability, weight variation and assay are found in the range specified; 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	4.86(±0.072)	5.41(±0.035)	0.31(±0.018)	2.28(±0.044)	98.45
F 2	4.90(±0.034)	5.37(±0.085)	0.26(±0.059)	2.97(±0.079)	99.92
F 3	4.95(±0.051)	5.52(±0.056)	0.36(±0.015)	3.63(±0.021)	101.41
F 4	4.78(±0.011)	5.28(±0.039)	0.33(±0.063)	2.56(±0.088)	97.47
F 5	4.84(±0.083)	5.63(±0.027)	0.30(±0.031)	3.48(±0.017)	98.45
F 6	4.93(±0.011)	5.29(±0.033)	0.38(±0.012)	3.93(±0.039)	99.20

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

The Carbamazepine (F3) 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.

The results of *in-vitro* drug release study for formulated sustained release tablets was described in Table 7 and Graphs were explain in Figure 5 and 6.

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Table 7: Cumulative *in-vitro* drug release study for trial batches of Carbamazepine 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	11.45	11.47	13.77	17.55	15.77	16.56
2	2	1.2	27.46	33.45	31.57	29.76	27.53	26.45
3	3	7.2	42.56	42.56	40.26	41.14	40.09	42.42
4	6	7.2	59.44	59.44	60.55	58.93	57.23	59.05
5	8	7.2	73.1	73.1	75.11	71.19	72.42	73.52
6	10	7.2	83.28	83.28	88.89	85.27	82.98	83.77
7	12	7.2	92.35	92.37	95.25	93.26	92.87	90.42

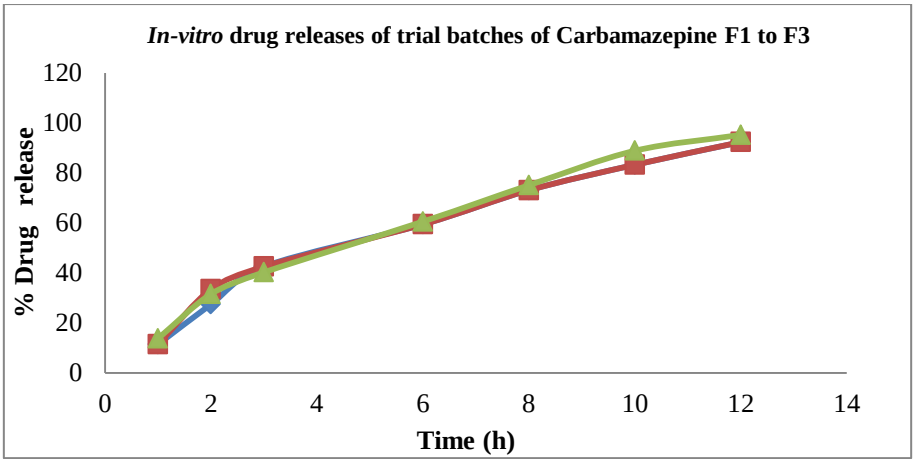

Figure 5: *In -vitro* drug releases of trial batches of Carbamazepine F1 to F3

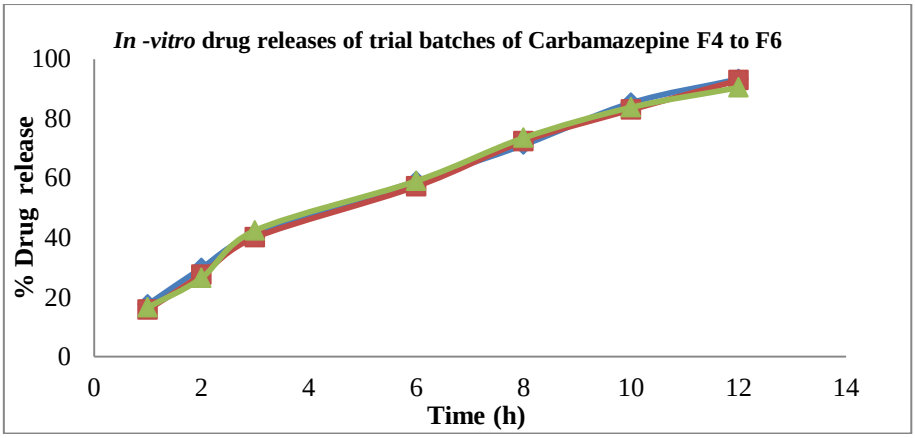

Figure 6: *In -vitro* drug releases of trial batches of Carbamazepine F4 to F6

From the findings of the dissolution analysis data interpreted as F3 batch of Carbamazepine shows 95.25% means 190.50 mg Carbamazepine release in 12 h. Hence, from dissolution analysis and physical evaluation results F3 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 [Elias NM et al., 2012][Hasanuzzaman M et al., 2011]

The stability study of the Carbamazepine tablet (F3) 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. The result of stability analysis of Carbamazepine for physical analysis was described in Table 8 whiles the results of *in-vitro* analysis in Table 9 and Figure 6.

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Table 8: Physical stability analysis of Carbamazepine F3 batch

Sr. No	Evaluation Test	Initial	End of 1st month	End of 2 nd month	End of 3 rd month
1.	Thickness (mm)	4.95(±0.051)	4.93(±0.027)	4.90(±0.011)	4.97(±0.062)
2.	Hardness (kg /Cm^2)	5.52(±0.056)	5.50(±0.061)	5.48(±0.015)	5.57(±0.043)
3.	Friability (%)	0.36(±0.015)	0.48(±0.027)	0.39(±0.059)	0.42(±0.041)
4.	Percentage weight variation	3.63(±0.021)	2.94(±0.064)	3.12(±0.048)	2.67(±0.027)
5.	Assay (%)	101.41	101.32	101.26	101.00

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

Table 9: *In-vitro* drug release study for stability of Carbamazepine F3 batch

Sr. No.	Time (h)	pH of medium	Amount of drug released	Percentage drug release
1	1	1.2	26.24	13.12
2	2	1.2	61.26	30.63
3	3	7.2	82.34	41.17
4	6	7.2	117.76	58.88
5	8	7.2	148.44	74.22
6	10	7.2	175.30	87.65
7	12	7.2	188.46	94.23

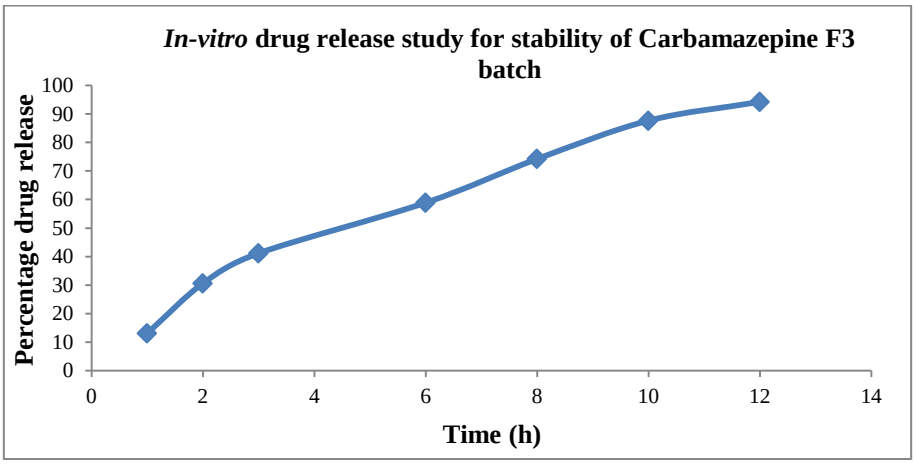

Figure 6: *In-vitro* drug release study for stability of Carbamazepine F3 batch

The results of stability study for optimized Carbamazepine F3 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 [Das U and Hossain MS, 2012][Shrestha P et al., 2014]

Table 10: Kinetic analysis for the F3 optimised batch of Carbamazepine tablets

Model Fitting	R^2	T-test	k	Interpretation
Zero order	0.9545	7.836	0.0913	Passes
1st order	0.9551	7.892	-0.0009	Passes
Matrix	0.9868	14.924	0.2691	Passes
Peppas	0.9872	15.167	0.1757	Passes
Hixsen-crowell	0.9549	7.874	-0.0003	Passes
Best fitted model: Peppas				
Parameters for Korsmeyer-Peppas Equation				
n =				0.7153
k =				0.1757

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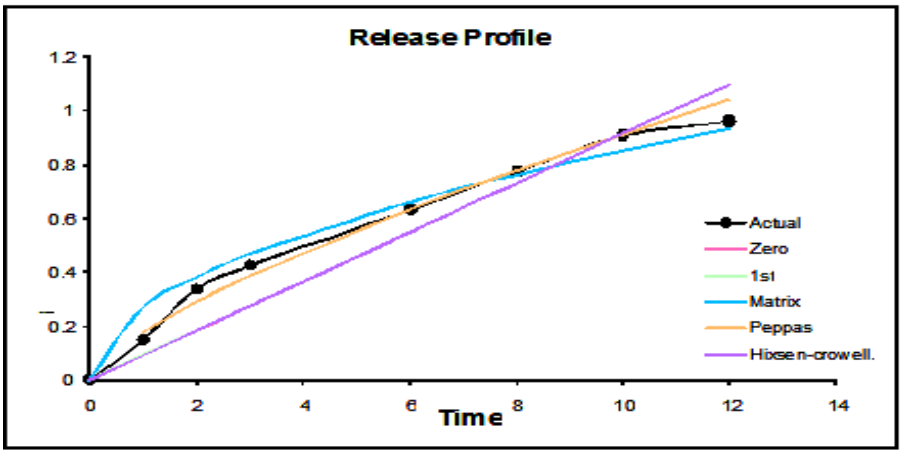

Figure 8: Kinetic graphs for F3 optimised batch of Carbamazepine tablets

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 $0.7153 < n < 1$ is indicative of anomalous transport or non - Fickian diffusion.

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. Carbamazepine release (F3 batch show 95.25%) was much faster from ethyl cellulose than Eudragit RS 100 coating. 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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