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Effects of disintegrant pellets on Indapamide sustain release tablet formulated by reservoir technique

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ABSTRACT

In this study tablets prepared by using three different types of pellets i.e. Indapamide drug pellets, Indapamide coated pellets and disintegrant pellets shows independent influence on the formulation. Drug release from reservoir pellets coated with ethyl cellulose and Eudragit RS 100 was depends on the thickness of coating and compaction pressure. Segregation is the problem, which can be minimizing by using disintegrant pellets in the formulation that gives the better understanding of formulation factors. HPMC K4M and MCC pH 101 were use as a binder in all formulations, PEG 400 as plasticizer, magnesium stearate and talc as lubricant. The percentage drug release of batch F3 was show 88.86 means 2.221 mg of Indapamide release in 12 h and all the physical evaluation results were within the prescribed limits. The metformin sustain release F3 batch showed non-Fickian diffusion kinetics.

Keywords: Disintegrant pellets, Ratio of pellets, Sustained release tablets, Matrix tablets, Characterization of pellets

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INTRODUCTION

Pellets can be defined as small, free flowing, spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment. Pellets offer a high degree of flexibility in the formulation and development of sustain release dosage forms. Coated pellets formulation is the preferred because of various advantages but compression of coated pellets is a challenging task. It required optimization of formulation and processing variables. The key formulation variables are composition, porosity, size, shape and density of the pellets, types and amount of polymer coating and nature, size and amount of tabletting excipients. The pellet core should be strong with some degree of plasticity. It should be highly porous with an irregular shape. [1]

The major aims of this work included preparation of different types of three different types of pellets (drug, soft and disintegrant pellets) and their combination as a model to investigate the ability of the mixture to form disintegrating tablets, physical evaluation of all three different pellets. After preparing, the pellets formulate optimized sustained release multiple unit tablets using various ratios of different pellets. Finally, characterisations of drug release from optimized tablets and investigate the influence of storage conditions on drug release from reservoir pellets in tablets. One of the ways to design sustains release systems are to coat spherical pellets with a polymer that regulates their drug release rate. As MCC beads are insoluble hence adsorption of drugs which reduces the release rate. Their strong osmotic activity could result in faster and higher water uptake. These have consequently increased the tensile stress on the membrane. Finally, dilute the drug concentration inside the pellets leads to efflux of drugs. [2] In the first part of this work, different types of pellets were prepared and evaluate for physical characterization. Moreover, in the second part the prepared Indapamide tablets evaluated based on *in- vitro* release.

EXPERIMENTAL SECTION

Indapamide obtained as a gift sample from Glenmark Pharmaceutical Industry, Nashik. Crospovidone, HPMC K4M, MCC pH 101 and all other chemicals and reagents were of analytical grade.

3. Experiment and method

3.1 Preparation of pellets [3], [4]

3.1.1 Drug pellets (step I): The drug-loaded pellets were prepared by layering the drug-binder solution on non-pareil beads using the composition described in Table 1. Initially mixture of Indapamide was pouring in plasticizer PEG 400 to make primary core as first layer solution. Second layer was formulating by spraying 20% HPMC K4M and 30% MCC pH 101 in ethanol as surface core material. Finally, these prepared drug pellets dried overnight and analysed.

Table 1: Formulation of Indapamide loaded pellets

Ingredients	FA1
Indapamide	2.5 mg (100%)
HPMC K4M	0.500 mg (20%)
MCC pH 101	0.833 mg (30%)
Magnesium stearate	0.05 mg (2%)
PEG 400	0.025 mg (1%)
Talk	0.075 mg (3%)
Ethanol	q.s

3.1.2 Disintegrant Pellets (step II): Disintegrants pellets were prepared by using Crospovidone (5% w/w) a super disintegrant. Crospovidone and the plasticizer PEG 400 mixed in ethanol. In this mixture, 20% HPMC K4M and 30% MCC pH 101 added and disintegrants pellets were prepared by layering the drug binder solution on nonpareil beads and dried for overnight. Prepared disintegrant pellets evaluated for further investigation.

Table 2: Formula for preparing disintegrant pellets using Crospovidone

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

3.1.3 Preparation of drug-loaded coating pellets or soft pellets (step III): A mixture of ethyl cellulose 10cps plasticizer PEG 400 and talc mixed. This solution was layered on drug Indapamide uncoated pellets. Same process repeated for Indapamide uncoated pellets using Eudragit RS 100. The coating level calculated from the weight difference between the coated and the uncoated pellets. The coating efficiency (percentage) calculated from the actual weight gain of the coated pellets divided by the theoretical weight gain.

Table 3: Formula for Indapamide coated pellets using ethyl cellulose and Eudragit RS100

Ingredients	FAC 1	FAC 2	FAC 3	FAC 4	FAE 1	FAE 2	FAE 3	FAE 4
Indapamide	Indapamide uncoated pellets FA1							
Ethyl Cellulose 10 cps	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

3.2 Evaluation of Pellets prepared in step I, II and III [5], [6]

3.2.1 Size distribution/Sieving method: 50 g of sample weighed and placed on top sieve of mechanical sieve shaker. The sieves were removing and the granules retained on each sieve weighed. The percentage weights of powder retained on each sieve were calculated.

Weight size = Mean size of sieve opening **x** % Weight retained on smaller sieve ..... (01)

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

3.2.2 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.

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

3.2.4 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 measurement of bulk density, size and shape, surface area, moisture content and cohesiveness of materials. Compressibility index and Hausner's ratio 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 were calculate as follows:

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

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

3.2.5 Angle of repose: Angle of repose was determining by the funnel techniques. 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 was measure 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.

RESULTS AND DISCUSSION

4.1 Compression of coated pellets [9], [10], [11]

The final Indapamide tablet prepare by using different ratio of pellets i.e drug, disintegrant and soft pellets as mention in step I, II and III. On the basis, different composition of these pellets trail batches were evaluated and optimized batches examined for further investigation as follows:

A. Drug–excipient interaction studies
B. Flow properties
- Bulk density
- Tapped density
- Carr's index
- Hausner's ratio
- Angle of repose

C. Weight variation
D. Thickness
E. Hardness and friability
F. Drug content determination (Assay)
G. In-*Vitro* release studies (Dissolution test)
H. Analysis of dissolution data using Kinetic models

Table 4: Sieve analysis of pellets [12], [13]

Sieve analysis	Sieve Number	Mean size opening (3)	Weight retain (over size)	% Weight retain (over size) (5)	Weight size 3× 5
Indapamide uncoated pellets	Sieve 40/60	337.5	6.50	13.0	4387.50
	Sieve 60/ 80	215	8.45	16.9	3633.50
	Sieve 80/100	165	20.30	40.6	6699.00
	Fine	125	14.75	29.5	3687.50
Crospovidone 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
Ethyl cellulose coated Indapamide pellets	Sieve 40/60	337.5	5.90	11.80	3982.50
	Sieve 60/ 80	215	7.25	14.50	3117.50
	Sieve 80/100	165	22.58	45.16	7451.40
	Fine	125	14.27	28.54	3567.50
Eudragit RS100 coated Indapamide pellets	Sieve 40/60	337.5	6.80	13.60	4590.00
	Sieve 60/ 80	215	8.24	16.48	3543.20
	Sieve 80/100	165	21.21	42.42	6999.30
	Fine	125	13.75	27.50	3437.50

Particle size = weight size /100

The three different types of pellets Indapamide drug pellets, soft pellets(Indapamide coated with ethyl cellulose 10 cps and Eudragit RS100) and disintegrant pellets pass through #60 and retain on #100 i.e. particle ranging 150-350 micron. All the pellets satisfied the requirements of sieve analysis and used for further investigation.

Table 5: Physical evaluation for pellets [14], [15]

Pellets	Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index	Hausner's ratio	Angle of repose
Indapamide uncoated pellets	FA1	0.492 (±0.052)	0.645 (±0.079)	23.72 (±0.095)	1.31 (±0.052)	24.15 (±0.012)
Crospovidone 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)
Ethyl cellulose coated Indapamide pellets	FAC1	0.495 (±0.032)	0.566 (±0.061)	12.54 (±0.011)	1.143 (±0.035)	22.26 (±0.021)
	FAC2	0.486 (±0.075)	0.592 (±0.096)	17.90 (±0.025)	1.218 (±0.067)	23.61 (±0.045)
	FAC3	0.502 (±0.096)	0.595 (±0.023)	15.63 (±0.039)	1.185 (±0.025)	26.41 (±0.013)
	FAC4	0.490 (±0.042)	0.587 (±0.031)	16.52 (±0.074)	1.197 (±0.033)	24.78 (±0.034)
Eudragit RS100 coated Indapamide pellets	FAE 1	0.501 (±0.067)	0.629 (±0.042)	20.34 (±0.055)	1.255 (±0.027)	22.28 (±0.011)
	FAE2	0.484 (±0.034)	0.633 (±0.093)	23.53 (±0.062)	1.307 (±0.083)	22.61 (±0.055)
	FAE3	0.476 (±0.078)	0.617 (±0.067)	22.85 (±0.031)	1.296 (±0.074)	24.51 (±0.053)
	FAE4	0.472 (±0.091)	0.609 (±0.086)	22.49 (±0.053)	1.290 (±0.040)	24.98 (±0.022)

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

The physical evaluation of all the pellets for bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose these results are satisfactory and within the prescribe range indicates good flowability and compressibility. These pellets are then used for formulating sustain release tablets using various combination and ratio.

4.2 Drug content and percentage assay for uncoated drugs pellets [16]

Table 6: Drug content and percentage assay for uncoated drugs

Pellets	Formulation code	Drug content (mg)	Assay (%)
Indapamide	FA1	2.46	98.40

The drug content and percentage assay of uncoated pellet are within the prescribed as per pharmacopeia.

4.3 Scanning electron microscopy for appearance [17], [18], [19], [20], [21]

SEM is a qualitative tool for the assessment of size, shape, morphology, porosity, size of pellets or distribution and consistency of compressed dosage forms. The information obtained from SEM can correlate to assess dissolution behavior, bioavailability and crystalline structure. The images also help analysts determine where the particles are maintain desired physical characteristics during processing including after compaction.

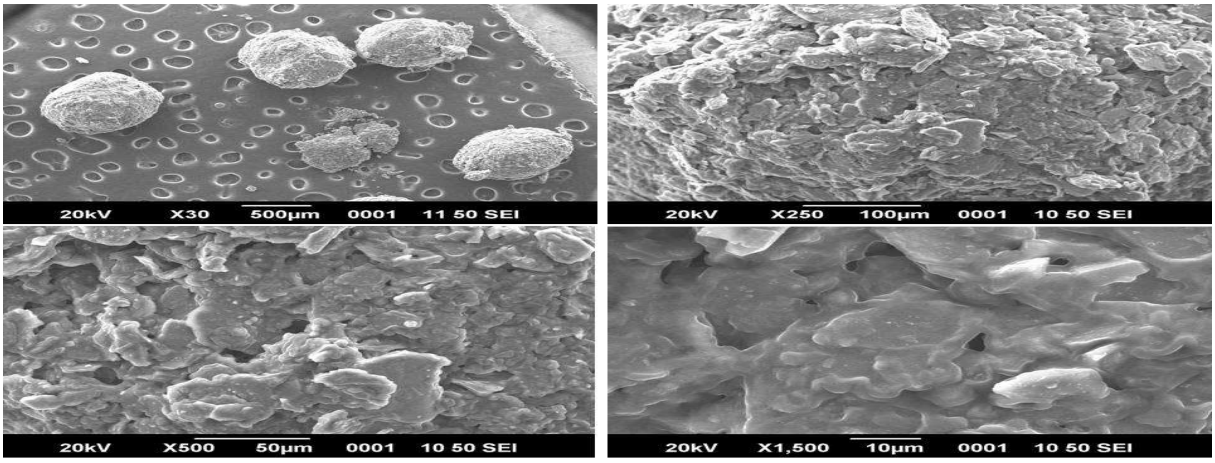

Figure 1: SEM for Indapamide uncoated pellets FA 1

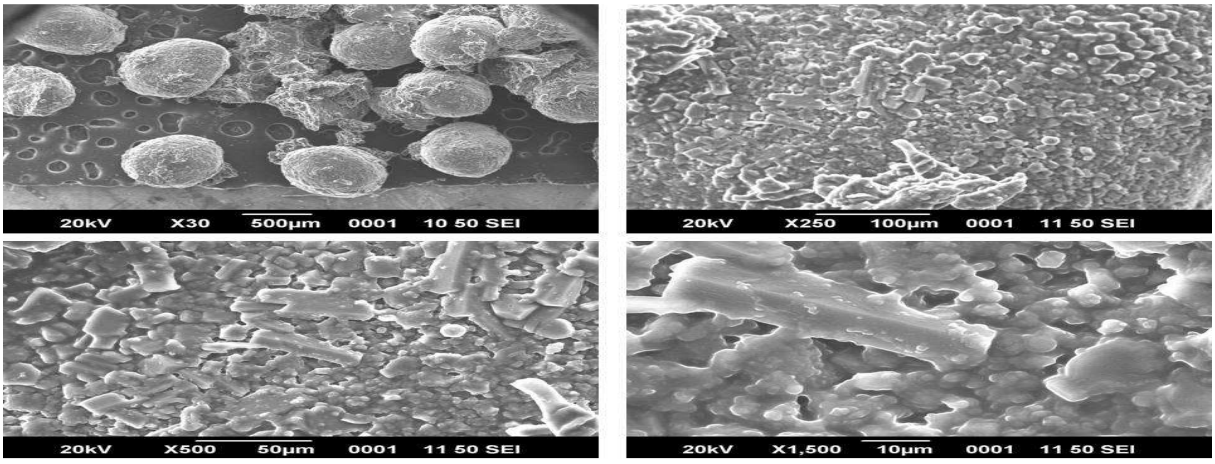

Figure 2: SEM for optimized Indapamide coated pellets

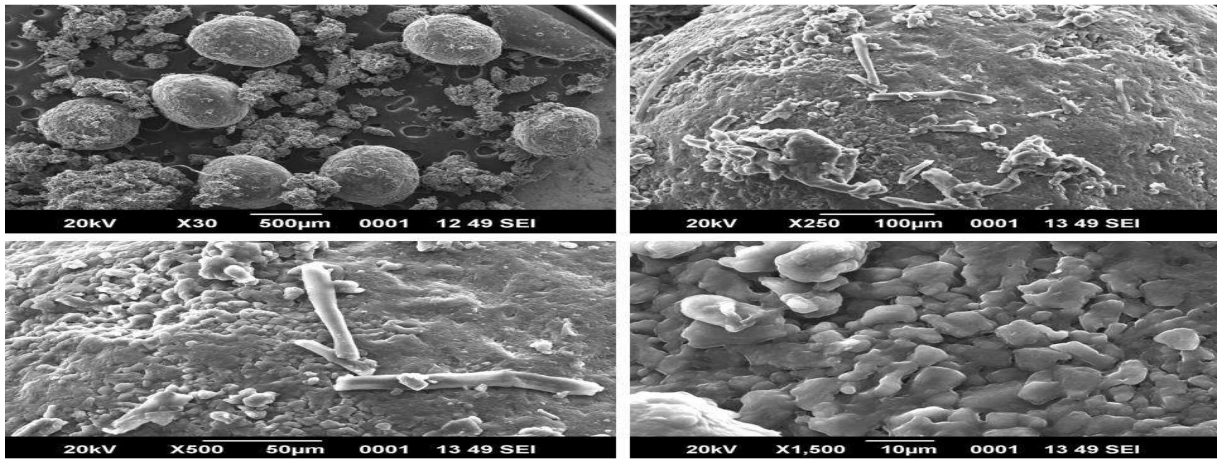

Figure 3: SEM for Crospovidone disintegrant pellets

The observed maintenance of the surface morphology and topography of the tablet coating is an indication of the stability of the coated layer. Visually the figure shows similar appearance and indicates no change in physical parameters.

4.4 Fourier transform infrared spectroscopy (FTIR) for drug-polymer interaction [22-24]

FTIR study of drug and excipients carried out to determine the interaction between them. The IR spectrum of Indapamide, Ethyl Cellulose, Crospovidone and Optimized Indapamide formulation recorded in the stretching frequency range 400-4000 cm^{-1}. The samples prepared by KBr (Potassium Bromide) press pellet technique.

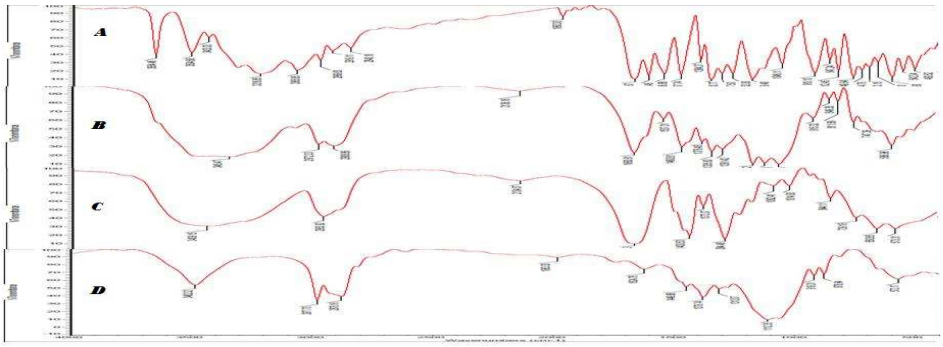

Figure 4: Compatibility studies of drug Indapamide and polymers by FTIR spectroscopy, A: Pure Indapamide, B: Indapamide Tablet, C: Cross providone, D: Ethyl Cellulose

Table 7: Data obtained from compatibility studies of drug Indapamide and polymers by FTIR

Important IR spectral peaks of different groups expressed in wave number (cm^{-1})			
Indapamide Pure drug	**Interpretation**	**Stretching**	**Indapamide tablets**
3433.03	3400–3250 (m)	N–H stretch	3345.47
3065.85	3000–2850 (m)	C–H stretch	2972
1661.67	1680–1640 (m)	–C=C– stretch	1660.61
1169.40	1300–1150 (m)	C–H wag (–CH2X)	1166.42
910.10	1000–650 (s)	=C–H bend	915.32
847.24	1000–650 (s)	=C–H bend, O–H bend, N–H wag, C–H "oop", C–Cl stretch, C–H rock, –C≡C–H: C–H bend	849.35
586.93		Alkyl halides	586.96

The FTIR spectra of the drug and polymer combination compared with the spectra of the pure drug indicating the stability of the drug during pelletization process and no shifting of peaks significantly found in final formulation.

4.5 Evaluation of tablets for post compression properties [25-27]

The post compression study includes thickness, hardness, friability, weight variation and assay are found in the range specified. The results are show in Table 8.

Table 8: Evaluation of optimized tablets for compression properties

Preparation of tablet	**Formulation code**	**Average thickness (mm)**	**Average hardness (kg /cm^2)**	**Friability (%)**	**Percentage weight variation**	**Assay** (%)
Trial 3	F 1	3.34(±0.017)	5.1(±0.012)	0.69(±0.034)	3.46(±0.144)	95.52
Trial 8	F 2	3.43(±0.011)	5.0(±0.020)	0.64(±0.035)	3.71(±0.132)	97.56
Trial 11	F 3	3.31(±0.017)	5.5(±0.018)	0.38(±0.020)	2.45(±0.060)	100.16
Trial 15	F 4	3.42(±0.005)	5.4(±0.011)	0.55(±0.036)	3.05(±0.028)	103.54
Trial 20	F 5	3.33(±0.005)	5.5(±0.057)	0.54(±0.005)	2.91(±0.051)	101.73
Trial 24	F 6	3.41(±0.023)	5.3(±0.015)	0.62(±0.043)	2.75(±0.160)	99.35

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

The post compression study includes thickness, hardness, friability, weight variation and assay are found in the range specified. Hence sustain release tablet satisfy the criteria of pharmacopeia.

Table 9: Cumulative *in- vitro* drug release for trial batches of Indapamide F1 to F6

Sr. No.	**Time (h)**	**pH of medium**	**% Drug Release for F1**	**% Drug Release for F2**	**% Drug Release for F3**	**% Drug Release for F4**	**% Drug Release for F5**	**% Drug Release for F6**
1	1	1.2	10.23	10.69	11.22	10.98	11.65	10.89
2	2	1.2	21.42	19.22	20.57	22.32	24.34	24.05
3	3	7.2	34.65	31.08	33.80	36.11	37.45	33.75
4	6	7.2	55.12	47.23	49.73	51.64	54.67	49.87
5	8	7.2	65.98	59.49	60.97	62.52	66.43	62.73
6	10	7.2	72.37	72.76	74.44	73.33	78.23	74.11
7	12	7.2	80.45	82.67	88.86	84.85	86.9	83.5

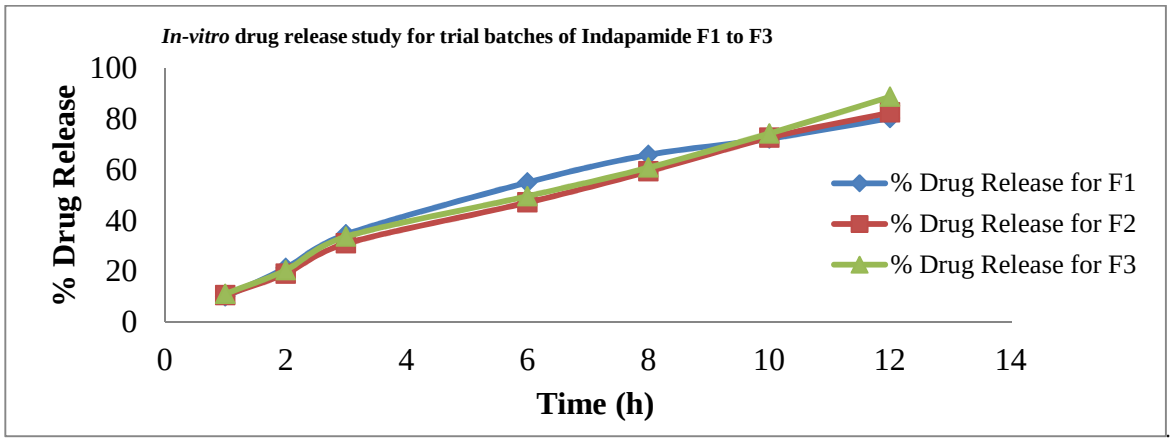

Figure 5: *In-vitro* drug release study for trial batches of Indapamide F1 to F3

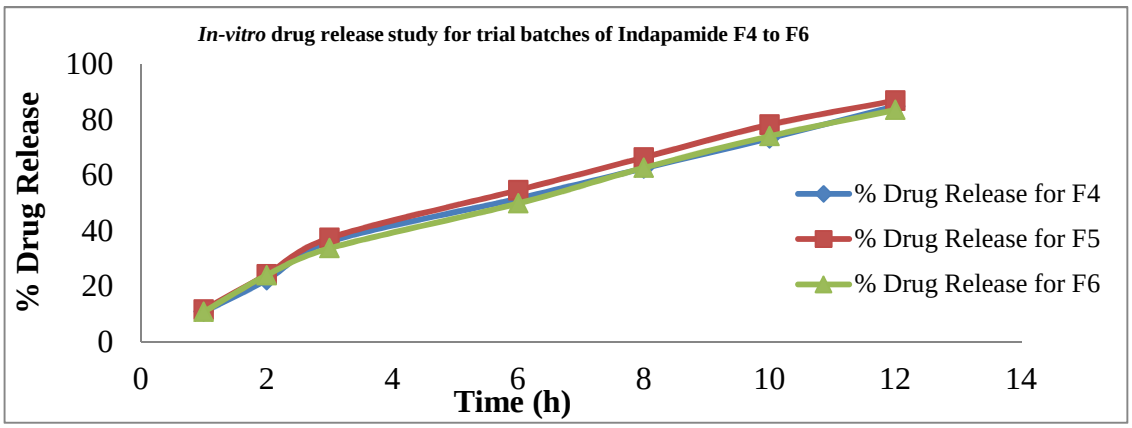

Figure 6: *In-vitro* drug release study for trial batches of Indapamide F4 to F6

From the release data and physical evaluation F3 batch, shows 88.86% means 2.221 mg of Indapamide release in 12 h and all the physical evaluation results were within the prescribed limits. Hence F3 batch used for further investigate as optimized batch.

4.6 *In- vitro* drug release study for stability of optimized tablets [28]

The stability studies of the tablets of F3 carried out according to ICH guidelines at 40±2^{O}C and 75±5 percentage relative humidity for three months by storing the samples in stability chamber. After the third months the results of *in-vitro* drug release study for stability of optimized tablets were satisfactory and within the prescribed range as given Table10 and 11.

Table 10: Evaluation test for Indapamide F3 for stability analysis at 40^{O}C and 75% relative humidity

Sr. No	Evaluation Test	Initial	End of 1stmonth	End of 2 nd month	End of 3 rd month
1.	Thickness (mm)	3.31(±0.017)	3.31(±0.024)	3.24(±0.067)	3.42(±0.082)
2.	Hardness (kg /Cm^2)	5.50(±0.180)	5.52(±0.056)	5.46(±0.088)	5.46(±0.063)
3.	Friability (%)	0.38(±0.020)	0.42(±0.011)	0.38(±0.043)	0.31(±0.048)
4.	Percentage weight variation	2.45(±0.060)	2.38(±0.041)	2.51(±0.059)	2.62(±0.076)
5.	Assay (%)	100.16	100.04	100.03	100.04

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

Table 11: *In – vitro* drug release study stability of Indapamide F3 at 40^{O}C and 75% relative humidity

Sr. No.	Time (h)	pH of medium	Amount of drug released	Percentage drug release
1	1	1.2	0.282	11.28
2	2	1.2	0.566	22.67
3	3	7.2	0.819	32.76
4	6	7.2	1.222	48.88
5	8	7.2	1.572	62.91
6	10	7.2	1.960	78.41
7	12	7.2	2.188	87.52

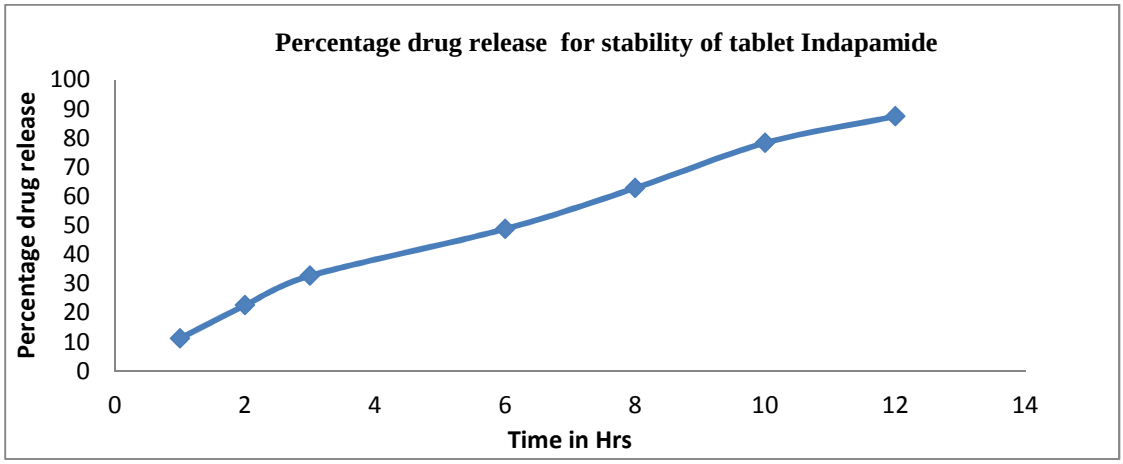

Figure 7: Percentage drug release for stability of tablet Indapamide

4.7 Kinetics of Indapamide drug release [29-31]

Table 14: Kinetic analysis for the F3 optimised batch of Indapamide tablet

Model Fitting	R^2	T-test	k	Interpetation
Zero order	0.9816	12.588	0.0236	Passes
1st order	0.9817	12.622	-0.0002	Passes
Matrix	0.9727	10.262	0.0686	Passes
Peppas	0.9949	24.180	0.0389	Passes
Hix.Crow.	0.9817	12.611	-0.0001	Passes
Best fitted model: Peppas				
Parameters for Korsmeyer-Peppas Equation				
n =			0.7788	
k =			0.0389	

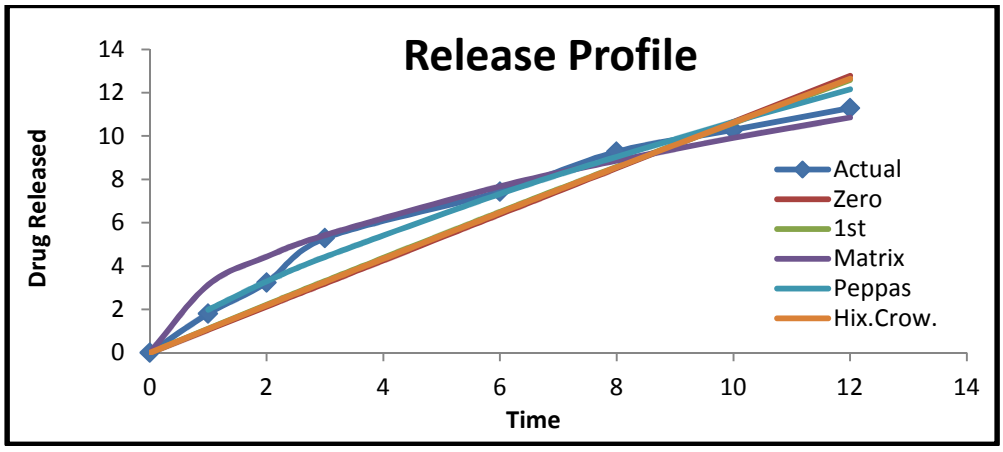

Figure 8: Kinetic graphs for F3 optimised batch of Indapamide tablet

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. The value of exponent n (0.7788) indicates of anomalous transport or non-Fickian diffusion. It therefore indicates a combination of diffusion and erosion. Since this value lies at the near

end of the range give, it tends to show majorly erosion behavior than Fickian release mechanism. When this observation coupled with that from above and conclusion can draw that, the predominant mechanism of release is erosion and the zero order release.

CONCLUSION

One of the challenge in the formulating of such tablets is maintaining the sustain drug release after compaction which can be change the structural in the coating and altered drug release. That may be due to formulation factors like thickness of coating and excipients. Segregation is the problems, which can be, minimize by using disintegrant pellets in the formulation gives the better understanding of formulation factors. Indapamide tablets prepared by using three different types of pellets i.e. drug pellets, coated pellets and disintegrant pellets shows independent influence on disintegrant used in formulation. The reservoir pellets coated with ethyl cellulose and Eudragit RS 100 shows the release is depends on the thickness of coating and compaction pressure.

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