ISSN 2349-7203

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

HUMAN

Human Journals
**Research Article**
July 2015 Vol.:3, Issue:4


# Preparation of Sustained Release Metformin Tablet from Reservoir Pellets

IJPPR
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An official Publication of Human Journals
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**Submission:** 7 July 2015
**Accepted:** 14 July 2015
**Published:** 25 July 2015



**Keywords:** Metformin tablet, reservoir pellets, Sustained release tablets, Characterization of pellets

**ABSTRACT**

In this study tablets prepared by using three different types of pellets i.e. Metformin pellets, coated Metformin pellets and disintegrant pellets were shown independent influence on the formulation. The reservoir pellets coated with ethyl cellulose and Eudragit RS 100 the release is depends on the thickness of coating and compaction pressure. HPMC K4M and MCC pH 101 used as a binder in all formulations, PEG 400 as plasticizer, magnesium stearate and talc as a lubricant. In the present study release data and physical evaluation of F9 batch shows 93.27% means 466.35 mg of Metformin release in 12 h and all the physical evaluation results were within the prescribed limits. The release of Metformin F9 batch was follows non-Fickian diffusion kinetics.

## 1. INTRODUCTION

This work shows the importance of some key factors to consider when designing sustained release tablets of Metformin coated multiparticulate (reservoir) which provides deeper information about release ability after compaction. Metformin tablets were prepared such a way to design oral modified release systems of coated pellets with polymers like ethyl cellulose and Eudragit RS 100 that regulates their drug release rate. Such reservoirs pellets compacted into sustained release tablets. The Metformin tablet normally intended to disintegrate into discrete pellets in the gastrointestinal tract and the drug subsequently is released in a controlled manner from the individual pellets [1].

The compression behaviour of the microcrystalline cellulose based pellets show optimum porosity. The regular size of pellets does not interact in tablet compression without damaging the tablet core hence the drug release could be maintained for longer time. Hear the physical properties of drug pellets, coated pellets and excipients can affects the reservoir pellets and it has equal importance in drug release to maintain sustained form. Reservoir pellets consisting of a drug-layered starter core and a water insoluble polymer coating to control the release of the active compound. Number of studies indicates the potential effects of the drug core on the release, the research to date focuses predominantly on the properties of the coating. After optimizing the parameters, coating applied on the drug using various concentrations of the polymer. The concentration of polymer optimized based on dissolution studies. Reproducible batches evaluated for physical characterization and release [2].

## 2. MATERIALS

Metformin obtained as a gift sample from Dr. Reddy's lab, Hyderabad. Crospovidone, HPMC K4M, MCC pH 101 and all other chemicals and reagents were of analytical grade.

## 3. METHODS

### 3.1 Preparation of pellets [3,4,5,6,7]

**3.1.1 Drug pellets (step I):** The Metformin 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 poured 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 used for further analysis.

**Table No. 1: Formulation of Metformin loaded pellets**

| **Ingredients** | **FB 1** |
|---|---|
| Metformin | 500 mg |
| HPMC K4M | 100 mg (20%) |
| MCC pH 101 | 150 mg (30%) |
| Magnesium stearate | 10 mg (2%) |
| PEG 400 | 5 mg (1%) |
| Talc | 15 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 were added. The 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% |
| Talc | 3% | 3% | 3% |
| Ethanol | q.s | q.s | q.s |

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

**Table 3: Formula for Metformin 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 |
|---|---|---|---|---|---|---|---|---|
| Metformin | Metformin uncoated pellets FB1 | | | | | | | |
| 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 [8,9,10]**

**3.2.1 Size distribution/Sieving method:** 50g of sample was weighed and placed on top sieve of mechanical sieve shaker. Then the sieves were removed and the granules retained on each sieve were 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 was determined by mercury pycnometer.

**3.2.3 Bulk density:** Accurately weighed quantities of the pellets were added to the cylinder with the aid of a funnel. Typically the initial volumes were 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.

**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 proposed 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 calculated as follows:

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

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

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

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

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

## 4. RESULTS

**4.1 Compression of coated pellets:** The final Indapamide tablet was prepared by using different ratio of pellets i.e. drug, disintegrant and soft pellets as mention in step I, II and III. On the basis of different composition of these pellets trail batches were evaluated and optimized batches were 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 for uncoated pellets**

| Sieve analysis | Sieve Number | Mean size opening (3) | Weight retain (over size) | % Weight retain (over size) (5) | Weight size 3× 5 |
|---|---|---|---|---|---|
| **Metformin uncoated pellets** | Sieve 40/60 | 337.5 | 5.90 | 11.80 | 3982.50 |
| | Sieve 60/ 80 | 215 | 9.25 | 18.50 | 3977.50 |
| | Sieve 80/100 | 165 | 23.58 | 47.16 | 7781.40 |
| | Fine | 125 | 11.27 | 22.54 | 2817.50 |
| **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 Metformin pellets** | Sieve 40/60 | 337.5 | 8.75 | 17.50 | 5906.25 |
| | Sieve 60/ 80 | 215 | 9.15 | 18.30 | 3934.50 |
| | Sieve 80/100 | 165 | 19.90 | 39.80 | 6567.00 |
| | Fine | 125 | 12.20 | 24.40 | 3050.00 |
| **Eudragit RS100 coated Metformin pellets** | Sieve 40/60 | 337.5 | 6.60 | 13.20 | 4455.00 |
| | Sieve 60/ 80 | 215 | 9.25 | 18.50 | 3977.50 |
| | Sieve 80/100 | 165 | 21.90 | 43.80 | 7227.00 |
| | Fine | 125 | 12.25 | 24.50 | 3062.50 |

**Particle size = weight size /100**

**Table 5: Physical evaluation for pellets**

| Pellets | Formulation code | Bulk density ($g/cm^3$) | Tapped density ($g/cm^3$) | Compressibility index | Hausner's ratio | Angle of repose |
|---|---|---|---|---|---|---|
| **Metformin uncoated pellets** | FB1 | 0.609 (±0.044) | 0.634 (±0.065) | 10.25 (±0.067) | 1.114 (±0.033) | 23.98 (±0.054) |
| **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 Metformin pellets** | FAC5 | 0.523 (±0.054) | 0.631 (±0.017) | 17.11 (±0.038) | 1.206 (±0.058) | 22.76 (±0.026) |
| | FAC6 | 0.526 (±0.066) | 0.644 (±0.075) | 18.32 (±0.027) | 1.220 (±0.021) | 23.43 (±0.032) |
| | FAC7 | 0.548 (±0.093) | 0.661 (±0.037) | 17.09 (±0.066) | 1.206 (±0.093) | 25.21 (±0.019) |
| | FAC8 | 0.511 (±0.072) | 0.633 (±0.046) | 19.27 (±0.073) | 1.238 (±0.030) | 25.67 (±0.013) |
| **Eudragit RS100 coated Metformin pellets** | FAE5 | 0.477 (±0.045) | 0.581 (±0.070) | 17.90 (±0.063) | 1.218 (±0.057) | 23.70 (±0.045) |
| | FAE6 | 0.468 (±0.021) | 0.576 (±0.034) | 18.75 (±0.074) | 1.230 (±0.031) | 22.44 (±0.062) |
| | FAE7 | 0.463 (±0.086) | 0.588 (±0.054) | 21.25 (±0.038) | 1.269 (±0.089) | 24.43 (±0.015) |
| | FAE8 | 0.474 (±0.045) | 0.592 (±0.032) | 19.93 (±0.045) | 1.248 (±0.034) | 25.61 (±0.063) |

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

**Table 6: Drug content and % assay for uncoated drugs**

| Pellets | Formulation code | Drug content (mg) | Assay % |
|---|---|---|---|
| Metformin | FB1 | 493 | 98.60 |

### 4.2 Scanning electron microscopy for appearance [11,12,13,14,15]

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 surface of Metformin pellets was smooth as observed in SEM micrographs. The difference between the surface roughness parameter derived from the analysis for formulations were statistically significant. Such difference could explain in terms of the particle size of the active ingredients. Metformin pellets were slightly more spherical, although no statistical difference between the types of pellets were notice and displayed a less rough surface.

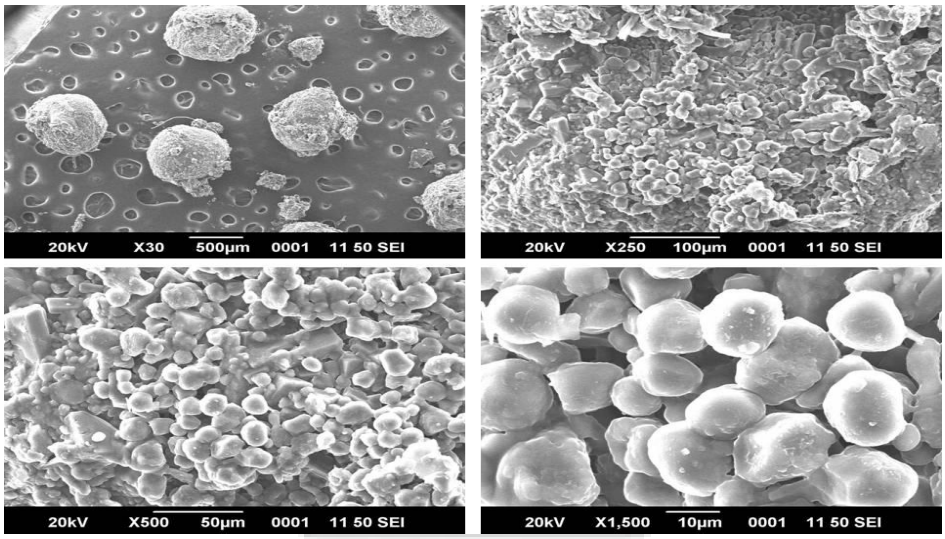


**Figure 1: SEM for Metformin uncoated pellets FB 1**

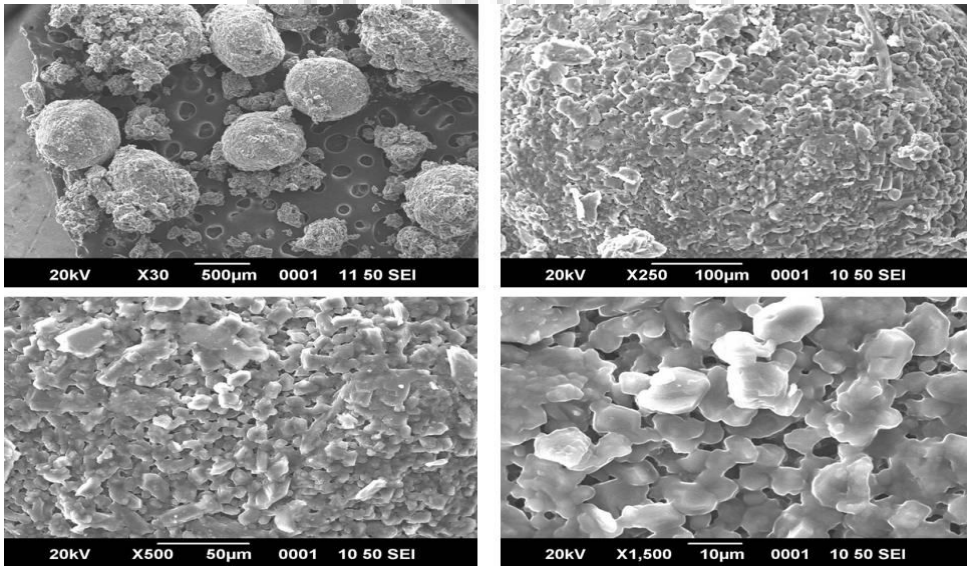


**Figure 2: SEM for optimized Metformin coated pellets**

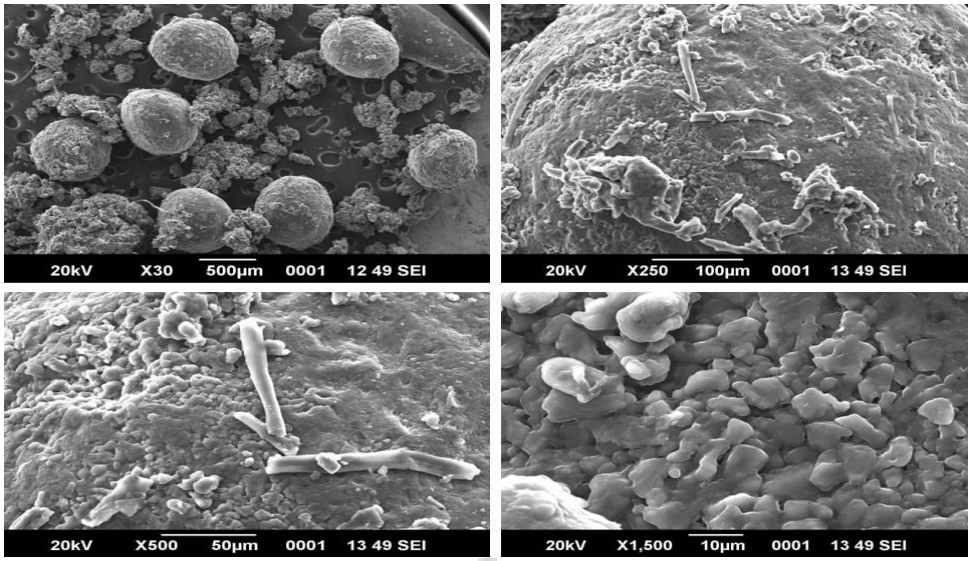


**Figure 3: SEM for Crospovidone disintegrant pellets**

### 4.3 Fourier transform infrared spectroscopy (FTIR) study for drug- polymer interaction [16,17,18,19]

FTIR study of Metformin and excipients carried out to determine the interaction between them. The IR spectrum of pure Metformin drugs, Eudragit RS100, Crospovidone and optimized formulation recorded in the stretching frequency range 400-4000 $cm^{-1}$. The samples prepared by KBr (Potassium Bromide) press pellet technique. The results tabulated in Table 7.

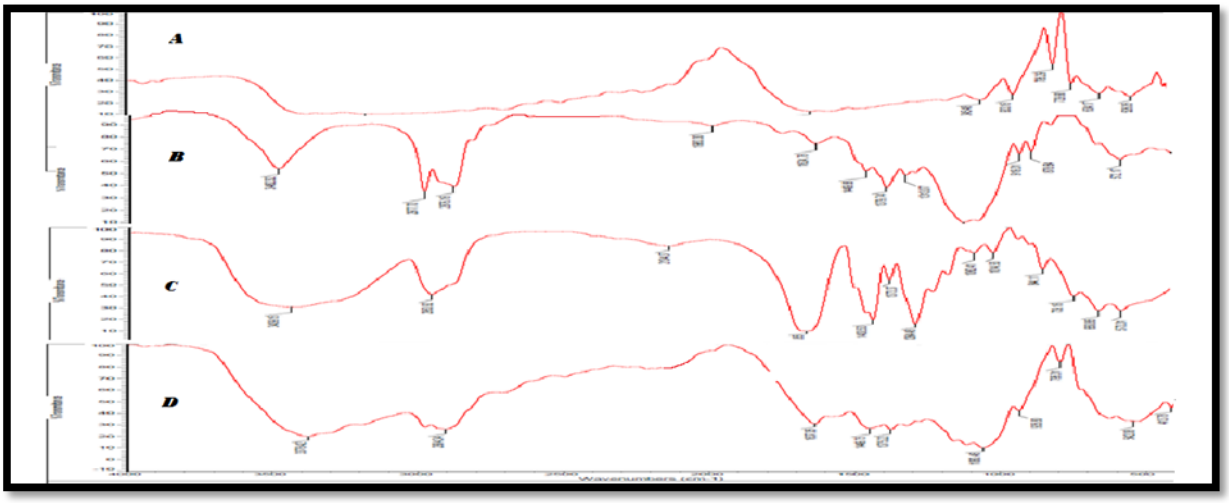


**Figure 4: Compatibility studies of drug Metformin and polymers by FTIR spectroscopy, A: Pure Metformin, B: Ethyl Cellulose, C: Crosprovidone, D: Metformin Tablet**

**Table 7: Data obtained from compatibility studies of drug Metformin and polymers by FTIR spectroscopy**

| Important IR spectral peaks of different groups expressed in wave number ($cm^{-1}$) | | | |
|---|---|---|---|
| **Metformin bands** | **Interpretation** | **Stretching** | **Metformin tablets** |
| 1632.53 | 1650–1580 | N–H bend | 1637.05 |
| 1045.48 | 1250–1020 | C–N stretch | 1060.46 |
| 933.16 | 950–910 | O–H bend carboxylic acids | 935.80 |
| 796.29 | 850–550 | alkyl halides stretch | 795.31 |
| 634.17<br>526.05 | 690–515 | C–Br stretch | 542.08 |

### 4.4 Evaluation of tablets for post compression properties [20,21,22]

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

**Table 8: Evaluation of optimized tablets for compression properties**

| Preparation of tablet | Formulation code | Average thickness (mm) | Average hardness (kg /cm2) | Friability (%) | Percentage weight variation | Assay (%) |
|---|---|---|---|---|---|---|
| Trial 26 | F 7 | 5.42(±0.045) | 5.22(±0.072) | 0.29(±0.027) | 3.12(±0.012) | 98.24 |
| Trial 31 | F 8 | 5.76(±0.052) | 5.17(±0.038) | 0.37(±0.043) | 3.71(±0.017) | 101.2 |
| Trial 35 | F 9 | 5.47(±0.034) | 5.20(±0.021) | 0.22(±0.016) | 2.45(±0.023) | 99.15 |
| Trial 39 | F 10 | 5.45(±0.067) | 5.41(±0.028) | 0.26(±0.083) | 2.91(±0.063) | 98.09 |
| Trial 44 | F 11 | 5.42(±0.042) | 5.32(±0.057) | 0.43(±0.012) | 3.62(±0.051) | 98.25 |
| Trial 48 | F 12 | 5.55(±0.076) | 5.61(±0.025) | 0.67(±0.035) | 2.65(±0.062) | 98.73 |

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

**Table 9: Cumulative *in – vitro* drug release study for trial batches of Metformin F7 to F12**

| Sr. No. | Time (h) | pH of medium | Percentage drug release F7 | Percentage drug release F8 | Percentage drug release F9 | Percentage drug release F10 | Percentage drug release F11 | Percentage drug release F12 |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1.2 | 13.25 | 12.65 | 12.52 | 11.75 | 11.65 | 13.22 |
| 2 | 2 | 1.2 | 28.65 | 24.66 | 26.73 | 27.33 | 25.32 | 24.75 |
| 3 | 3 | 7.2 | 37.15 | 36.96 | 37.28 | 37.56 | 35.73 | 36.72 |
| 4 | 6 | 7.2 | 60.54 | 61.20 | 60.58 | 59.43 | 61.89 | 65.55 |
| 5 | 8 | 7.2 | 74.45 | 75.29 | 77.71 | 74.10 | 73.49 | 77.22 |
| 6 | 10 | 7.2 | 86.12 | 85.15 | 87.95 | 82.23 | 84.66 | 84.87 |
| 7 | 12 | 7.2 | 92.21 | 91.64 | 93.27 | 88.89 | 92.50 | 92.81 |

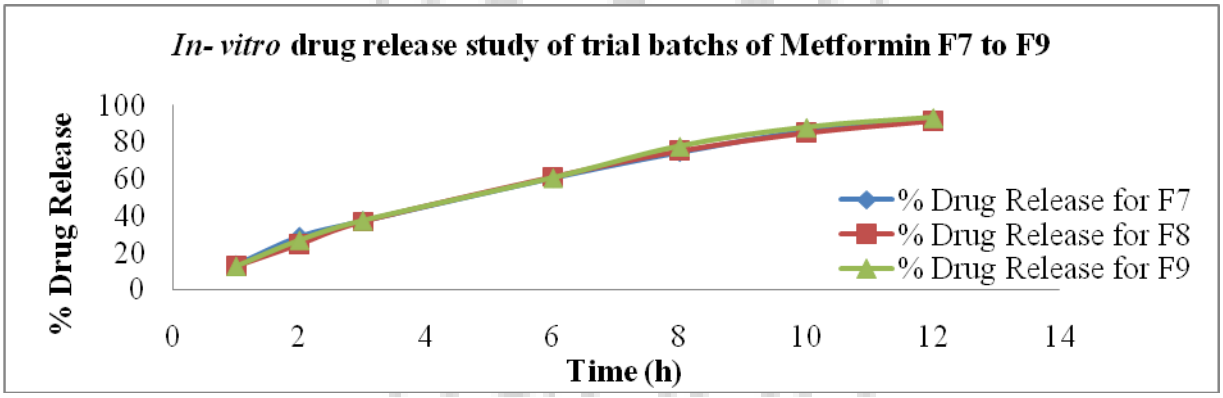


**Figure 5: *In- vitro* drug release study for trial batches of Metformin F7 to F9**

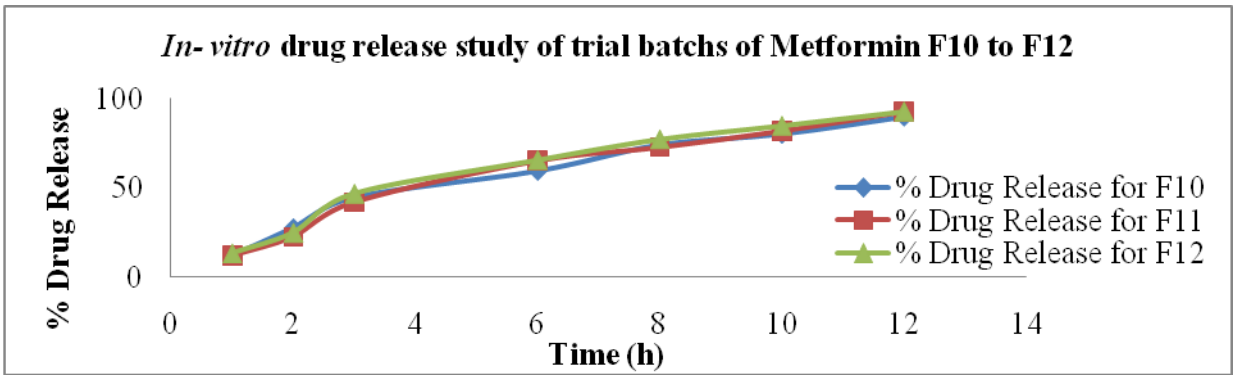


**Figure 6: *In- vitro* drug release study for trial batches of Metformin F10 to F12**

From the release data and physical evaluation F9 batch, shows 93.27% means 466.35 mg of Metformin release in 12 h and all the physical evaluation results were within the prescribed limits. Hence F9 batch used for further investigation as optimized batch.

**4.5 *In- vitro* drug release study for stability of optimized Metformin tablets [23,24]**

The stability study of the Metformin tablets of F9 optimised were carried out according to ICH guidelines at 40±2$^{o}$C/75±5% RH 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 Table 10 and 11.

**Table 10: Evaluation test for Metformin F9 for stability analysis at 40$^{O}$C and 75% relative humidity**

| Sr. No. | Evaluation Test | Initial | End of 1$^{st}$month | End of 2$^{nd}$ month | End of 3$^{rd}$ month |
|---|---|---|---|---|---|
| 1. | Thickness (mm) | 5.47(±0.034) | 5.47(±0.032) | 5.41(±0.056) | 5.45(±0.021) |
| 2. | Hardness (kg /Cm$^{2}$) | 5.20(±0.021) | 5.24(±0.056) | 5.13(±0.033) | 5.25(±0.052) |
| 3. | Friability (%) | 0.22(±0.016) | 0.32(±0.019) | 0.21(±0.062) | 0.38(±0.047) |
| 4. | Percentage weight variation | 2.45(±0.023) | 2.55(±0.076) | 2.41(±0.17) | 2.48(±0.88) |
| 5. | Assay (%) | 99.15 | 99.12 | 99.06 | 99.02 |

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

**Table 11: *In -vitro* drug release study stability of Metformin 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 | 61.900 | 12.38 |
| 2 | 2 | 1.2 | 128.650 | 25.73 |
| 3 | 3 | 7.2 | 219.800 | 43.96 |
| 4 | 6 | 7.2 | 295.550 | 59.11 |
| 5 | 8 | 7.2 | 380.200 | 76.04 |
| 6 | 10 | 7.2 | 417.250 | 83.45 |
| 7 | 12 | 7.2 | 465.100 | 93.02 |

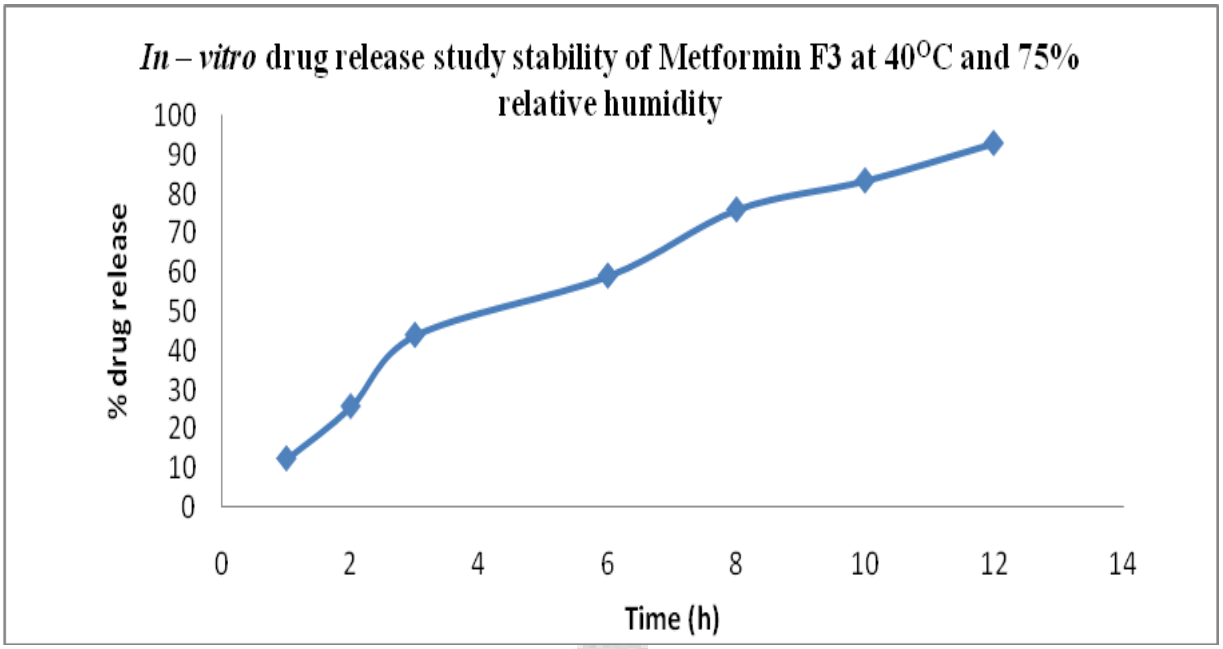


**Figure 7: Percentage drug release for stability of tablet Metformin**

**4.6 Kinetics of Metformin drug release** [25,,26,27]

**Table 12: Kinetic analysis for the F3 optimised batch of Metformin tablet**

| Model Fitting | R2 | T-test | k | Interpretation |
|---|---|---|---|---|
| Zero order | 0.9642 | 8.907 | 0.0018 | Passes |
| 1st order | 0.9642 | 8.909 | 0.0000 | Passes |
| Matrix | 0.9797 | 11.981 | 0.0053 | Passes |
| Peppas | 0.9924 | 19.756 | 0.0031 | Passes |
| Hix.Crow. | 0.9642 | 8.908 | 0.0000 | Passes |
| **Best fitted model: Peppas** | | | | |
| **Parameters for Korsmeyer-Peppas Equation** | | | | |
| **n** = 0.7734 | | | | |
| **k** = 0.0031 | | | | |

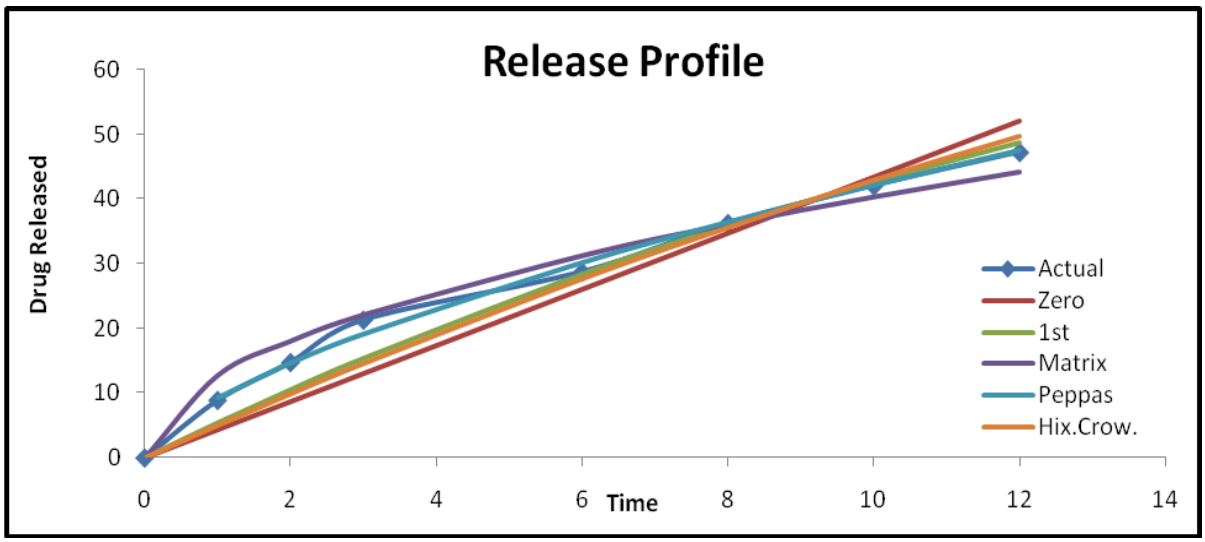


**Figure 8: Kinetic graphs for F3 optimised batch of Metformin tablet**

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 values of exponent n (0.7734) indicates of anomalous transport or non - Fickian diffusion. Therefore it indicates a combination of diffusion and erosion. Since this value lies at the near end of the given range, it tends to show majorly erosion behavior than Fickian release mechanism. When these observations coupled with that from above, draw a final conclusion that the predominant mechanism of release is erosion and the zero order kinetic.

## 5. DISCUSSION

The three different types of pellets Metformin drug pellets, soft pellets Metformin coated with Ethyl cellulose 10 cps and disintegrant pellets pass through #60 and retain on #100 i.e. particle ranging 150-350 micron. Bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose these results are satisfactory and within the prescribed range, indicate good flowability and compressibility. The surfaces of all pellets were smooth observed in SEM micrographs indicate no change in physical parameters.

The FTIR spectra of the Metformin and polymer combination compared with the spectra of the Metformin indicating the stability of the Metformin during pelletization process and no shifting of peaks significantly found. The post-compression study of sustained release Metformin tablets includes thickness, hardness, friability, weight variation and assay are found in the specified

range. Among all batches F9 shows 93.27% means 466.35 mg of Metformin release in 12 h and shows non - Fickian diffusion Kinetic.

## 6. CONCLUSION

The major aim of this work was to identify the major parameters affecting drug release from matrix coated pellets. Varying the type of the polymer had a higher impact on release. Metformin release was much faster from ethyl cellulose coating and this was attributed to the higher polymer permeability. The drug release was shown drug partition into the polymer and hence that release was related with permeability of the matrix.

The compression behaviour of the microcrystalline cellulose based pellets show optimum porosity. The regular size of pellets does not interact in tablet compression without damaging the tablet core hence the drug release could be maintained for longer time. The physical properties of drug pellets, coated pellets and excipients can affect the reservoir pellets and it has an equal importance to maintain sustained drug release. The assessment of the release kinetics revealed that drug release from reservoir pellets was found to be non-Fickian type controlled release.

## ACKNOWLEDGMENT

The authors are grateful to Sophisticated Test & Instrumentation Centre, Cochin University of Science and Technology, Cochin - 682 022, Kerala, India, for giving evaluation support in the research work.

## 7. REFERENCES

1. A.G. Ozturk, S.S. Ozturk, B.O. Palsson, T.A. Wheatley and J.B. Dressman. Mechanism of release from pellets coated with an ethylcellulose- based film. J Cont Res, 1990; 14: 203-213.
2. Nicklasson F and Alderborn G. Modulation of the tabletting behaviour of microcrystalline cellulose pellets by the incorporation of polyethylene glycol. Eur J Pharm Sci, 1999; 9: 57-65.
3. Srujan Reddy, Palash Das, Harika Das and Arpita Ghosh. MUPS (Multiple Unit Pellet System) Tablets - A Brief Review. J Pharm Bio Sci, 2011; 12 (02): 1-5.
4. F. Podczeck, P.E. Knight and J.M. Newton. The evaluation of modified microcrystalline cellulose for the preparation of pellets with high drug loading by extrusion/spheronization. Int J Pharm, 2008; 350: 145–154.
5. Guanhao Ye, Siling Wang, Paul Wan Sia Heng, Ling Chen and Chao Wang. Development and optimization of solid dispersion containing pellets of Itraconazole prepared by high shear pelletization. Int J Pharm, 2007; 337: 80–87.
6. Nantharat Pearnchob and Roland Bodmeier. Coating of pellets with micronized ethylcellulose particles by a dry powder coating technique. Int J Pharm, 2003; 268: 1-11.
7. Nasim Sadri Alamdari, Zahra Jafari Azar, Jaleh Varshosaz, Solmaz Ghaffari, Sanaz Ghaffari and Farzad Kobarfard. Preparation and evaluation of sustained release pellets of Tramadol. African Journal of Pharmacy and Pharmacology, 2012; 6(28): 2123-2132.

8. F.O. Costa, A.A.C.C. Pais and J.J.S. Sousa. Analysis of formulation effects in the dissolution of Ibuprofen pellets. Int J Pharm, 2004; 270: 9–19.
9. Fasiuddin Arif Mohammed, A.Arunachalam, G.Venkatarami Reddy, V.Pallavi, SK.Moulali and T.V.Tulasi Rama Raju. Formulation and evaluation of Carbamazepine extended release tablets USP200mg. Int J Bio Pharm Res, 2012; 3(1): 145-153.
10. H. Santos, F. Veiga, M. Pina, F. Podczeck and J. Sousa. Physical properties of chitosan pellets produced by extrusion - spheronisation: influence of formulation variables. Int J Pharm, 2002; 246: 153-169.
11. Kai Pan, Xing Tang and Jianhong Yang. Preparation of sustained release pellets of poorly soluble drugs by cogrinding and extrusion-spheronisation. Asian Journal of Pharmaceutical Sciences, 2009; 4 (2): 106-114.
12. Hiroto Bando and James W. McGinity. Relationship between drug dissolution and leaching of plasticizer for pellets coated with an aqueous Eudragit® S100:L100 dispersion. Int J Pharm, 2006; 323: 11–17.
13. Gihan Nabil Fetih. Formulation and characterization of Gelucire pellets for sustain release of Ibuprofen. Bull. Pharm. Sci., Assiut University, 2010; 33(2): 217-224.
14. Balagani Pavan Kumar, Irisappan Sarath Chandiran and Korlakunta Narasimha Jayaveera. Formulation development and evaluation of Glibenclamide loaded Eudragit RLPO microparticles. International Current Pharmaceutical Journal, 2013; 2(12): 196-201.
15. He Wei, Du Qing, Cao De-Ying, Xiang Bai and Fan Li-Fang. Study on colon-specific pectin/ethyl cellulose film-coated 5-fluorouracil pellets in rats. Int J Pharma, 2008; 348: 35–45.
16. Pintu K De, Jibitesh Paul, Sanjoy K Dey, Subas C Dinda and Soumen Rakshit. Formulation, Physico-chemical characterization and release kinetic study of antihypertensive Transdermal Patches. Der Pharmacia Sinica, 2011; 2 (5): 98-109.
17. Gowda D. V., Khan M. S and Nagendra R. Spray dried Indapamide microparticles for controlled release- A novel approach. Int J Pharma and Bio Sci, 2010; 1(4): 459-463.
18. Thulasi V Menon and C.I.Sajeeth. Formulation and evaluation of sustained release sodium alginate microbeads of Carvedilol. Int J Pharm Tech Res, 2013; 5(2): 746-753.
19. U Rajesh Kini, Deepak Kamath and Mahalaxmi Rathnanand. Formulation and evaluation of Carbamazepine extended release tablet by controlled erosion technology. Int J Pharm Pharm Sci, 2012; 4(4): 345-351.
20. Lourdes Ochoa, Manuela Igartua, Rosa Ma, Hernández, Alicia R. Gascón and José Luis Pedraz. Preparation of sustained release hydrophilic matrices by melt granulation in a high-shear mixer. J Pharm Pharmaceut Sci, 2005; 8(2): 132-140.
21. Magdalena Stevanovi, Aleksandra Radulovi, Branka Jordovi, and Dragan Uskokovi. Poly (DL-lactide-co-glycolide) nanospheres for the sustained release of Folic acid. Journal of Biomedical Nanotechnology, 2008; 4: 1–10.
22. Utpal Das, Shimul Halder, Abul Kalam Lutful Kabir, Harun Rashid and Abu Shara Shamsur Rouf. Development and *in vitro* Evaluation of Sustained ReleaseMatrix Tablets of Indapamide from Methocel® K15 MCR and K100 LVCR. Dhaka Univ. J Pharm Sci, 2011; 10(2): 87-92.
23. Amol R. Jipkate, Chandrakant G. Bonde and R. T. Jadhav. Formulation and Evaluation of Citicoline Sustained Release Tablet. J Pharm Sci & Res, 2011; 3(1): 911-917.
24. Golam Kibria, KM Ariful Islam and Reza-Ul Jalil. Stability study of Ambroxol Hydrochloride sustained release pellets coated with acrylic polymer. Pak J Pharm Sci, 2009; 22(1): 36-43.
25. Urmi Das and Mohammad Salim Hossain. Effects of release modifier on Carvedilol release from Kollidon SR based matrix. International Current Pharmaceutical, 2012; 1(8): 186-192.
26. U Rajesh Kini, Deepak Kamath and Mahalaxmi Rathnanand. Formulation and evaluation of Carbamazepine extended release tablet by controlled erosion technology. Int J Pharm Pharm Sci, 2012: 4(4): 345-351.
27. Gautam Singhvi and Mahaveer Singh. Review: In- Vitro drug release characterization models. International Journal of Pharmaceutical Studies and Research, 2011; II (I): 77-84.