# "Formulation and Evaluation of Sustained Release Matrix Tablets of A Selective Antihypertensive Drug"

[1]Pritam Deshmukh, [2]Prof. Shrikant D Mahajan

[1,2]Maharashtra Institute of Pharmacy, (B-Pharm) Betala, Bramhapuri, Chandrapur, Maharashtra- 441206 (India)

**Abstract:** The present study was aimed at formulating and evaluating sustained release matrix tablets of Furosemide**,** an angiotensin II receptor type 1 antagonist, to enhance its therapeutic efficacy by maintaining a consistent plasma drug concentration over an extended period. Sustained release formulations are designed to release the drug at a predetermined rate to maintain a constant drug level for a specific duration. In this work, matrix tablets were prepared using the direc**t** compression method with varying concentrations of chitosan and sodium alginate, in combination with other release-retardant polymers. This study showed that the specific surface area of coating material MT has an effect on the flow properties of MT powder blends and the particle size of coating material MT affects the drug release from MT tablets. It was found that the liquid load factor ($L_f$) has an effect on the flow properties of MT powder blends but had no significant effect on the drug release from MT tablets. It was observed that aging had no significant effect on the hardness and dissolution profile of Feurosamide MT compacts.

**Keywords:** Matrix Tablet, liquid load factor, STD curve, Anti-hypertensive, Petaloid crystal

## INTRODUCTION

Sustained release dosage forms are the substances which initially release drug sufficiently to provide therapeutic effect soon after administration and further a gradual release over an extended period oftime[1]. Not all drug candidates are suitable for the preparation of sustained release dosage forms. The understanding of the certain parameters are very essential in the development of sustained release dosage forms, those are mainly drug physico-chemical characteristics such as, aqueous solubility, partition coefficient, ionization constant, drug stability[2] and biological parameters viz., absorption, distribution, metabolism, excretion, biological half life, therapeutics of drug in vivoenvironment[3] and also dose size and dosage frequency. Matrix Systems Matrix devices consist of drug dispersed homogenously throughout a continuous phase of polymer or lipid.[4] The device can be prepared either by the compression of polymer/drug mixture. Preparation of matrix tablets are widely been used now a days due to least complicated approach for retarding the release rate of drugs over an extended period of time[5] because their formulation is simpler, inexpensive, easy to produce5 and they have good in vitro-in vivo correlation. A matrix system is capable of accommodating both low and high drug loading active ingredients with a wide range of physical and chemical properties.[6]

Based up on types of release retardants the matrix systems are divided into two categories such

a. Hydrophilic matrix systems

b. Hydrophobic matrix systems

### Hydrophilic Matrix systems9

The hydrophilic matrix systems are the homogeneous dispersions of drug and hydrophilic polymers.[7] In these systems the primary rate limiting ingredients are hydrophilic polymers. When the hydrophilic matrix systems are exposed to aqueous environment or biological medium, the solvent penetrates into the free space between the macromolecule chains of the polymer and may undergo relaxation process due to stress of penetrated solvent; the polymer chain become more flexible and decrease in glass transition temperature results conversion of glassy polymer into rubbery phase leads to swelling and form a gelatinous layer on the surface of the system.[8] The gel layer becomes thicker and it depends up on the time with continuous penetration of water into the system. The thickness of this region is a critical factor in drug release process and essentially depends on the viscosity of the polymer[9]. The drug release from the gelatinous layer is swelling matrix[10] and decreased surface area at the penetrating solvent front. As the gel layer becomes thicker, the distance that the drug must cover increases, which decreases its release rate. Also the rate of drug availability is controlled by the rate of penetration of the distribution of the fluid into

the matrix,[11] this in turn controlled by the porosity of the matrices, surface area availability and adhesion between adjacent particles as well as size and shape of the particles[12]. There are several other factors which affect the drug release from the hydrophilic matrix systems those are grade, viscosity and type of the hydrophilic polymer (synthetic or natural or combinations etc), drug to polymer ratio, drug solubility, molecular weight of the drug and drug dose etc. In matrix frameworks with different systems, the drug molecule seems to be better supported for a sustained drug release profile.[13]

## MATERIAL & METHODS

The microporous polypropylene (void space 70% v/v) and microporous polylactic acid (void space 60% v/v) were gifts from ENKA AC Obernburg. The furosemide was provided by Hoechst (W994). The additives in the tablet were all of Dutch Pharmacopoeia quality. Other chemical Matrix tablet were all of analytical grade. The HPLC equipment consisted of a Waters ssociates pump M45, an auto-injector WISP 710 B and a Z-module, with a FBondapack Cl8 insert (8 x 100 mm), both of Waters Associates. The fluorimeter was a Shimadzu RF-530. The flame photometer was a Perkin Elmer 460 (emission 589.6 nm, slit 0.7 nm). The dissolution equipment consisted of a water bath with 6 vesse Matrix tablet, paddles, etc., designed according to the specifications of the USP XX, a pneumatic Rheodyne 6 position valve, an 8 channel Ismatec tubing pump, a Shimadzu UV190 spectrophotometer (330 nm) with a 3 mm quartz flow-through cell, an Apple PC He and a controlling interface. Furosemide was provided by Rasino Drugs Pvt. Ltd. Propylene glycol, microcrystalline cellulose, colloidal silicon dioxide calcium silicate magnesium alumino metasilicate and sodium starch glycolate were obtain from central store MIP Belata. All other reagents were of analytical grade and used without further purification.

### Methods

The formulation design of Matrix Tablet systems was done in accordance with a mathematical model. In this study, PG was used as a liquid vehicle, MCC was used as carrier material and three different coating material Matrix tablet were used. The concentration of the drug in solvent was kept constant in all formulations. According to this model, the carrier and coating powder material Matrix tablet can retain only certain amounts of liquid while maintaining acceptable flow ability and compressibility.

Firstly, the excipient ratio R of the powder is defined as,

$$R = Q / q$$

Where R is the ratio of the weight of carrier (Q) and coating (q) material Matrix tablet present in the formulation.

Secondly, the liquid load factor (Lf) is defined as the ratio of the weight of liquid medication (W) to the weight of the carrier material (Q) in the system. This ratio can be correlated with the flow and the compression properties of a given Matrix Tablet system. Lf is defined as,

$$Lf = W / Q$$

**Table no.1: Formulation design of Furosemide Matrix tablets (MT)**

| System | Furosemide (mg) | PG (mg) | MCC (mg) | CSD (mg) | MAMS (mg) | CS (mg) | SSG (mg) | Total (mg) |
|---|---|---|---|---|---|---|---|---|
| MT1 | 100.0 | 65.0 | 386.5 | 18.5 | - | - | 30.0 | 600 |
| MT 2 | 100.0 | 65.0 | 368.0 | 37.0 | - | - | 30.0 | 600 |
| MT 3 | 100.0 | 65.0 | 392.0 | 13.0 | - | - | 30.0 | 600 |
| MT 4 | 100.0 | 65.0 | 386.5 | - | 18.5 | - | 30.0 | 600 |
| MT 5 | 100.0 | 65.0 | 386.5 | - | - | 18.5 | 30.0 | 600 |
| MT 6 | 100.0 | 65.0 | 432.0 | 20.0 | - | - | 33.0 | 600 |
| MT 7 | 100.0 | 65.0 | 478.5 | 21.5 | - | - | 35.0 | 600 |
| MT 8 | 100.0 | 65.0 | 430.0 | 23.0 | - | - | 33.0 | 600 |

**Flow properties of Matrix Tablet systems**

The tapping method was used to investigate the flow properties of prepared Matrix Tablet powder blends. Bulk density measurements were carried by placing fixed weight of powder in graduated cylinder and volume occupied was measured and initial bulk density was calculated. 20 grams of the prepared powder blends were placed in a 50 mL cylinder. The cylinder was then tapped 1000 times at a constant velocity. The tapped density was determined on a tapped volume determination apparatus. Each analysis was carried out in triplicate. Weight variation, hardness, friability and content uniformity tests The prepared tablets were evaluated by carrying out tests for weight variation, hardness, friability and drug content uniformity. For estimating weight variation, 20 tablets were taken randomly from each tablet formulation and weighed individually. The average weight of all tablets and percentage deviation from the mean for each tablet were determined. The hardness of formulated tablets was assessed using a hardness tester and the mean hardness of three tablets was determined. The friability was determined on ten tablets using a friability tester and the percentage loss in weight was calculated. For drug content uniformity test, ten tablets were crushed individually and powder equivalent to 100 mg of clozapine was dissolved in 100 mL of methanol. The solution was then passed through a 0.45 µm nylon filter and analyzed using UV spectrophotometer at 284

nm after sufficient dilution with pH 4.5 acetate buffer.

**In vitro dissolution studies**

The USP apparatus II (paddle method) (DTB 678 equipment with thermostatic bath and circulation pump was used for all the in vitro dissolution studies. In this method, acetate buffer having the pH of 4.5 was used as dissolution media. The rate of stirring was 50 rpm. The dosage forms were placed in 900 mL of pH 4.5 acetate buffer maintained at 37 ± 0.5 ºC. At appropriate interval Matrix tablet (5, 10, 15, 20, 30 and 45 min), 5 mL of the samples were taken. The dissolution media was then replaced by 5 mL of fresh dissolution fluid to maintain a constant volume. After proper dilution, the samples were analyzed at 284 nm spectrophotometrically. The mean of three determinations was used to calculate the drug release from each of the formulations.

**Stability study**

The effect of aging on the hardness and dissolution of Matrix Tablet was determined by storing the tablets at 22 0C for up to 12 months. After that, the samples were tested for their dissolution profiles and hardnesses at the conditions that have been used with freshly prepared tablets. The results were compared with the freshly tested tablets.

**Procurement of Drugs:**

**Furosemide** As a gift sample from Torrent research centre, Ahmedabad.

**Instrumentation**

**UV-Visible double beam spectrophotometer with matched quartz cel Matrix tablet (1cm)**

- Model : UV 2450
- Make : Shimadzu, Kyoto, Japan
- Recording Range : - 3.99 to +3.99 Abs
- Photometric accuracy : ± 0.003Å
- Scanning range : 190–1100 nm
- Detector : silicon photodiode
- Software : UV probe 2.32

**RESULTS AND DISCUSSION**

**Flow properties**

Good flow properties are critical for larger scale production of tablet dosage forms. To evaluate the flow

properties of the prepared MT powder blends, Carr's index was calculated from the bulk and tapped densities of the blends. According to the USP, powders are considered to have passable flow properties if they have a Carr's index value of less than 25% (USP36-NF31, 2013). R value is an important formulation parameter for MT systems that may be optimized. The R values of MT-1, MT-2 and MT-3 were 20.9, 10.0 and 30.2 respectively. As shown in Table 2.2, MT-1 and MT-3 had fair flow properties because the formulations were containing high quantities of MCC and low quantities of colloidal silica. MT-2 exhibited passable flow properties because the formulation was containing high amounts of colloidal silica. As shown in Table the MT-1 had fair and MT-4 had good flow properties according to the Carr's index, but MT-5 exhibited poor flow properties. CS with its petaloid crystal structure and large micropores exhibited the smallest specific surface area which is lower than that of CSD with its loose particle aggregates. MAMS which is prepared by spray drying resulting in spherically shaped, porous, ultralight granules showed an almost 1.5 fold larger specific surface area than CSD (Hentzschel, 2011). MT-5 powder system prepared using CS showed poor flow properties, because CS has the lowest specific surface area in comparison to CSD and MAMS. This study showed that the nature of the coating agent and most likely its specific surface area has an effect on the flow properties of MT powders.

As shown in Table, the MT-1 and MT-6 had fair and MT-7 and MT-8 had good flow properties according to the Carr's index. It was found that there is a relationship between $L_f$ and the flow properties of MT powder blends. The MT systems with low $L_f$ values have better flow properties. This can be explained by the fact that, the MT systems with high $L_f$ values contain high amounts of liquid and low quantities of powder excipient. In contrast, the MT systems with low $L_f$ values contain high amounts of carrier material (MCC) and low quantities of liquid.

**Table no.2: Flow properties of Matrix tablet (MT) powder blends**

| System | Carr's index (%) | Type of flow |
|---|---|---|
| MT-1 | 19.8 ± 0.3 | Fair |
| MT-2 | 24.6 ± 0.3 | Passable |
| MT-3 | 16.5 ± 0.7 | Fair |
| MT-4 | 11.5 ± 0.4 | Good |
| MT-5 | 30.0 ± 0.4 | Poor |
| MT-6 | 17.6 ± 0.7 | Fair |
| MT-7 | 15.2 ± 0.8 | Good |
| MT-8 | 15.5 ± 0.5 | Good |

**Weight variation, friability, hardness and content uniformity tests**

The results of weight variation, friability, hardness and drug content are represented in Table. Average weight of MT tablets ranged from 598 ± 2 mg to 748 ± 2 mg.

All the Furosemide MT tablets had acceptable friability as none of the tested formulae had percentage loss in tablet's weights that exceed 1%, aMTo no tablet was cracked, split or broken in either formula. Since all prepared tablets met the standard friability criteria, they are expected to show acceptable durability and withstand abrasion in handling, packing and shipment.

In general, formulation should be directed at optimizing tablet hardness without applying excessive compression force, while at the same time assuring rapid tablet disintegration and drug dissolution. In other words, tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing. The mean hardness of each MT tablet was determined and is presented in Table providing that all the MT tablets had acceptable hardness. All MT formulations have shown lower hardness compared with that of conventional formula (DCT). This was due to the presence of the liquid in the MT formulations that hinder the formation of the interparticle bonds (H-bonds in case of MCC) which are the main reason for the higher specific hardness obtained in DCT.

It was found that there is a relationship between R value and the hardness of the tablets. The R value was inversely proportional to the hardness of the tablets i.e., when the R value increases, the hardness of the tablet will decrease. This was obvious from the following results. MT-2 had R value equal to 10.0 and the mean hardness was 171 N. MT-3 had R value equal to 30.2 and the mean hardness was 104 N. This can be explained by that, increasing R value increases the amount of carrier powder (MCC) used which is a highly porous material and the amount of coating material (colloidal silica) will decrease and this subsequently leads to decreased hardness of the tablets. It was found that there is a relationship between $L_f$ and the hardness of the tablets in the MT formulation having approximately the same R value. The $L_f$ was inversely proportional to the hardness of the tablets i.e., when the $L_f$ increases, the hardness of the tablets will decrease. This was obvious from the following results. MT-1, MT-6, MT-7 and MT-8 were having $L_f$ 0.427, 0.382, 0.345 and 0.315 and the mean hardness of them was 120, 123, 167 and 194 N, respectively. This can be explained by that, increasing $L_f$ of the formulation increases the amount of solvent used and decreases the amount of the powder excipient and this subsequently decreases the hardness of the tablets.

It was clear from Table that all the investigated Furosemide MT tablets complied with the pharmacopoeial requirements as regard their content uniformity which was found to lie within the

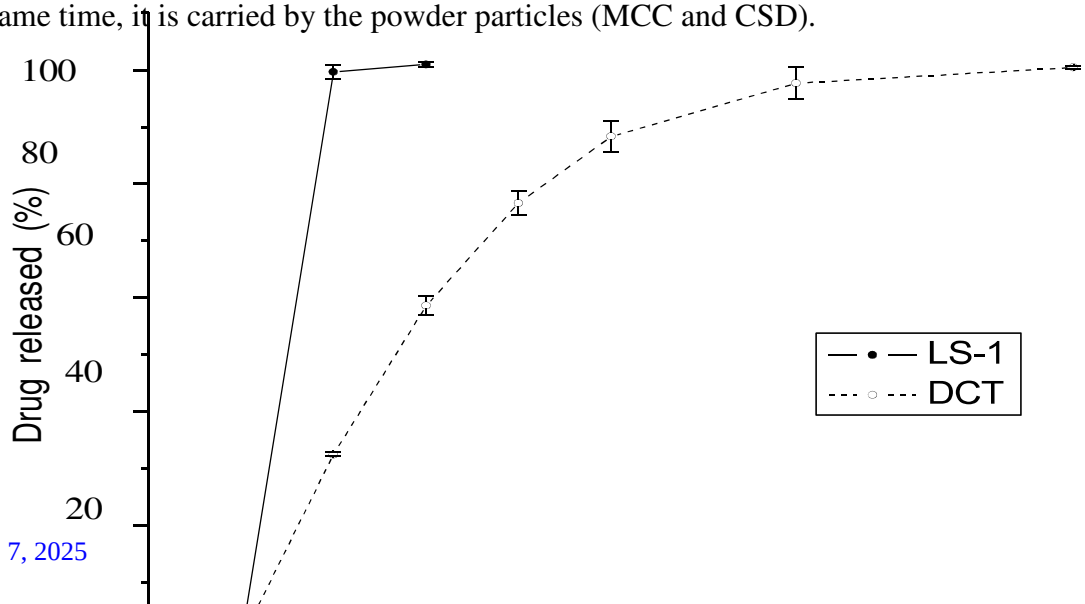
range 90-110%.

**Table no.3: Evaluation of Furosemide Matrix tablet (MT)**

| MT system | Hardness (N) | Friability | | Weight variation (mg) | Drug content (%) |
|---|---|---|---|---|---|
| | | Fines (%) | No. of broken tablets | | |
| MT-1 | 120 ± 2 | 0.25 | None | 599 ± 2 | 100 ± 2 |
| MT-2 | 171 ± 5 | 0.12 | None | 598 ± 2 | 98 ± 3 |
| MT-3 | 104 ± 8 | 0.34 | None | 600 ± 2 | 98 ± 5 |
| MT-4 | 124 ± 4 | 0.23 | None | 599 ± 1 | 100 ± 4 |
| MT-5 | 95 ± 7 | 0.14 | None | 599 ± 2 | 97 ± 5 |
| MT-6 | 123 ± 7 | 0.28 | None | 649 ± 4 | 99 ± 3 |
| MT-7 | 167 ± 8 | 0.18 | None | 699 ± 3 | 96 ± 5 |
| MT-8 | 194 ± 10 | 0.45 | None | 748 ± 2 | 99 ± 3 |
| DCT | 216 ± 6 | 0.45 | None | 549 ± 2 | 101 ± 3 |

**In vitro dissolution studies**

The dissolution profiles of Furosemide MT tablets (MT-1) and directly compressed tablets (DCT) in pH 4.5 acetate buffer are shown in Figure 2.1. Dissolution rates of MT tablets were compared with DCT. MT formulation showed greater release than DCT formulation. The percentages of drug released from MT-1 and DCT after 5 min were 99.6% and 32.5% respectively at pH 4.5 acetate buffer. This showed that the MT compacts produced faster dissolution rate in comparison with DCT. The enhanced dissolution rates of MT tablets compared to DCT may be attributed to the fact that, the drug is already in solution in PG, while at the same time, it is carried by the powder particles (MCC and CSD).



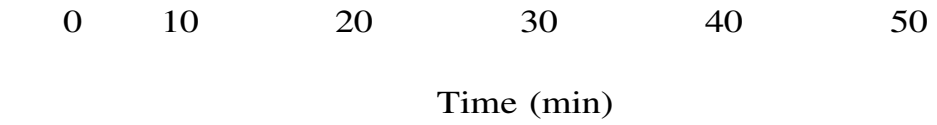
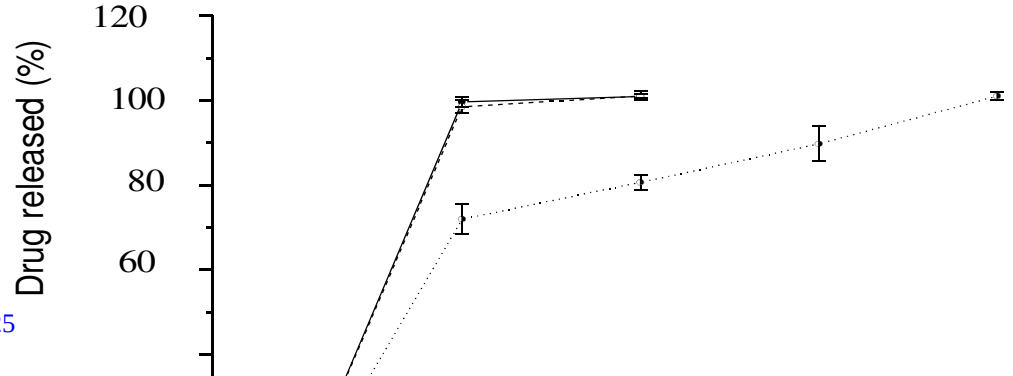



**Figure no. 1 Dissolution profiles of Furosemide from Matrix tablet and directly compressed tablets (means ± SD; n=3)**

The R value is an important parameter which is the ratio between the weights of the carrier and the coating material that may be optimized. An increase in the R value results in an enhanced release rate, if MCC and colloidal silica are used as carrier and coating materiaMT, respectively. MT compacts with high R values contain high amounts of MCC, low quantities of CSD and low liquid to powder ratios. This is associated with enhanced wicking, disintegration and thus, enhanced drug release. In contrast, if high amounts of colloidal silica are used, which means that the R value is low, the MT compact is overloaded with liquid formulation due to a high $L_f$. In such cases, even though drug diffusion out of the primary particles may be rapid, oversaturation might occur resulting in local precipitation or recrystallization of the drug and thus decreased release rates.

As shown in Figure 4, the MT formulations that had R values of 20.9 (MT-1) and 30.2 (MT-3) exhibited similar drug release profiles with small variations while the MT formulation that had low R value of 10.0 (MT-2) showed lower drug release. This study confirmed that the R value is an important parameter for MT systems and must be minimum 20 to obtain enhanced drug release.



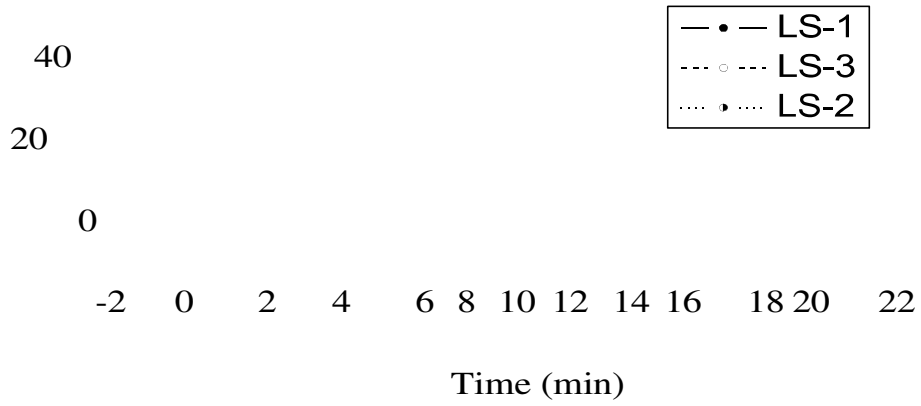



**Figure no.2 Dissolution profiles of Furosemide from Matrix tablet that had different R values (means ± SD; n=3)**

The dissolution profiles of Furosemide from MT tablets containing different coating materiaMT in pH 4.5 acetate buffer are shown in Figure 2.3. The dissolution test results showed that MT-1 containing CSD had the highest drug release compared with MT-4 containing MAMS and MT-5 containing CS. The particle size of CS (74 µm) is smaller than that of MAMS (100 µm), but is much higher than that of CSD (12 µm). Therefore the drug release from MT-5 was higher than that of MT-4, but was lower than that of MT-1 as expected. This study confirmed that the particle size of the coating materiaMT has an effect on the release of Furosemide from MT tablets and CSD is the best suitable coating material for preparing MT compacts of Furosemide.

**Stability study**

The effect of aging on the hardness and dissolution rate of MT tablets (MT-1) was determined by storing the tablets at 22 $^0$C for up to 12 months. The dissolution rate and hardness were measured for the MT tablets at the end of 3, 6 and 12 months. The results showed that storage at 22 $^0$C neither had an effect on the hardness (Table ) nor on the release profiles (Figure 2.5) of MT compacts. These results indicate that in the case of Furosemide the MT technology is a promising technique to enhance the release rate without having any stability issues.

**Table no.4:Hardness results of Furosemide Matrix tablet (fresh and aged)**

| MT system | Hardness (N) (fresh) | Hardness (N) (3 months) | Hardness (N) (6 months) | Hardness (N) (12 months) |
|---|---|---|---|---|
| MT-1 | 120 ± 2 | 110 ± 5 | 116 ± 6 | 114 ± 5 |

**Conclusion**

MT technique has been used successfully to produce a tablet dosage form of Feurosamide with faster dissolution rate than the regular tablet. Various tria MT were characterized based the blend and tablet parameters which showed the MT formulation containing MCC, CSD and SSG with Feurosamide dissolved in PG as a robust formula with required parameters. It showed significant increase in dissolution as compared DCT. It was found that there is a relationship between the carrier to coating material ratio (R value) and the in vitro release of Feurosamide from MT tablets. The R value was directly proportional to the in vitro release of Feurosamide from MT formulations. This study showed that the specific surface area of coating material MT has an effect on the flow properties of MT powder blends and the particle size of coating material MT affects the drug release from MT tablets. It was found that the liquid load factor ($L_f$) has an effect on the flow properties of MT powder blends but had no significant effect on the drug release from MT tablets. It was observed that aging had no significant effect on the hardness and dissolution profile of Feurosamide MT compacts. Although, better flow properties could be obtained using MAMS when compared to CSD, this former material resulted in slower dissolution rate. The MT -1 formulation was therefore considered optimal as it provided improve dissolution properties while being stable and robust to excipients modifications. In conclusion, this study showed that MT technique could be a promising strategy in improving dissolution of poorly water soluble drugs such as

Feurosamide and formulating immediate release dosage forms.

**REFERENCE**


1. Allan SH. The origins and evolution of controlled drug delivery systems. J. Controlled Release. 2008; 132(3): 153–163.
2. Allen TM, Hansen CB and Lopes de MDE. Pharmacokinetics of long-circulating liposomes. Adv. Drug Deliver. Rev. 1995; 16: 267- 284.
3. Andre IK andMukhopadhyay S. Response surface methodology. WIREsComput. Stat.2010; 2: 128-149.
4. Bagyalakshmi J, Sincy MP, Ravi TK. Development and optimization of RP-HPLC method for the estimation of s (-) amlodipine in tablet dosage form. Scholars Research Library, Der Pharma Chemica. 2011; 3 (4):140-145.
5. Bernard Bloom. Continuation of Initial Antihypertensive Medication after 1 Year of Therapy. Clin Ther. 1999; 20: 671–681.
6. Bernard Bloom. Continuation of Initial Antihypertensive Medication after 1 Year of Therapy. Clin Ther. 1999; 20: 671–681.
7. Rakesh Dayaram Tiwle Research Scholar (Pharmacy) Formulation And Optimization Of Ondansetron Hcl Fast-Dissolving Tablets Using Response Surface Methodology vol .3 issue 3. 2024.
8. Brahmankar D M, Biopharmaceutics and Pharmacokinetics- A Treatise, 2nd Ed., Published by VallabhPrakashan, New Delhi, India. 2008;343-350
9. Brahmankar D M. Biopharmaceutics and Pharmacokinetics- A Treatise, 2nd Ed., Published by Vallabh Prakashan, New Delhi, India, 2009, 397-405.
10. British Pharmacopoeia, British Pharmacopoeia Commission London, the Department of Health, Social Services and Public Safety, 2013; Volume I.
11. Cardinal JR. Matrix systems, In R.S. Langer, and D.I. Wise (eds.), Medical Applications of Controlled Release Vol I, Classes of Systems, CRC Press, Boca Raton, FL, USA, 1984; 41–67.
12. Chisato M, Hidetoshi S, Akira O and Akira Y.Design of nateglinide controlled release tabletcontaining erosion matrix tablet and multiple administration study in normal beagle dogs.Chem. Pharm. Bull.2009;57(9): 907—913.
13. Rakesh Tiwle, The Use Of Novel Polymers In A Drug Delivery & Its Pharmaceutical Application, Asian Journal Of Biochemical And Pharmaceutical Research Issue 2(Vol. 3) 2013 ISSN: 2231-256