Original Research Article

FORMULATION AND EVALUATION OF COLON SPECIFIC MELOXICAM MICROCAPSULES FOR THE TREATMENT OF ARTHRITIS

ABSTRACT

Objective: The main objective of the current study was to formulate and evaluate meloxicam-loaded microcapsules for colon-specific drug delivery using pH-dependent polymers. The emerging need for developing sustained release NSAIDs to minimize the dosing frequency was the main concern. Consequently, creating an oral sustained release formulation for the treatment of arthritis may be one method to get around this.

Methods: Eudragit RS/RL-100 polymers were used in emulsion solvent evaporation processes to create Meloxicam (MLX) microcapsules. Compatibility tests (FTIR), surface morphology by Scanning Electron Microscopy (SEM), yield, drug content, entrapment efficiency, and in vitro dissolution studies were performed on the produced MLX microcapsules.

Results: There was no interaction between the polymer and MLX, according to the IR spectra. The microcapsules were spherical in nature, which was confirmed by SEM. Normal frequency distribution MLX microcapsules were produced. The maximum drug entrapment efficiency of 94% was attained. The in vitro performance of MLX microcapsules demonstrated that the polymer concentration influenced sustained release. Furthermore, it was observed that the amount of polymer utilised regulated the release of the drug.

Conclusion: Based on the findings, it was concluded that one of the most promising formulation methods for creating colon specific drug delivery systems for the treatment of arthritis is the production of MLX microcapsules.

Keywords: Colon specific; Meloxicam; Arthritis, Emulsion solvent evaporation.

INTRODUCTION

The colon has a higher pH than the rest of the gastrointestinal tract (GIT) and this can be used as a modified release strategy. The most popular synthetic product employed in the production of colonic release formulations is Eudragit polymer, which has the potential to provide both pH-dependent release and mucoadhesiveness. Colonic delivery systems are composed of pH-independent and low permeability polymers or pH-dependent and permeable polymers must dissolve at a pH range of 6.0–7.0 in order to prevent degradation in the GIT and prolong the release of the medication before it reaches the colon.[1]

The colon specific drug delivery system (CDDS) protects the drug being delivered to the colon by preventing drug release and absorption in the stomach and small intestine of target drug delivery, as well as by preventing the bioactive agent from degrading in either of the dissolution sites. The gastrointestinal tract (GIT) has significant limitations in its ability to absorb medications orally, whereas CDDS is required to protect the body from the severe conditions of the upper GIT.[2]

Targeted drug delivery to the colon involves a combination of one or more controlled release mechanisms; the drug is delivered orally and releases rapidly in the colon but just at all in the upper region of the GIT. When treating local or systemic chronic disorders, there would be numerous advantages in terms of increased safety and less toxicity from specifically delivering the medicine to the colon.[3]

A lot of things need to be carefully considered for colonic drug administration to be successful, including the drug's characteristics, the kind of delivery device, and how the drug interacts with a healthy or sick gut. For example, the medication must first dissolve in the colon's luminal contents, whether a systemic or local effect is needed.[4] Due to the medications' inability to reach the site of action at the proper quantities, the majority of traditional drug delivery methods for treating colon problems are failing.

Meloxicam (MLX), 4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2- benzothiazine-3-carboxamide 1,1-dioxide pertains to the enolic acid group of oxicam derivatives. In addition to having an elimination half-life of almost 20 hours, it shows poor water solubility and a low dissolution rate (nearly 4.4 µg/mL at water). It is frequently used to treat acute pain, inflammation, and stiffness brought on by ankylosing spondylitis and rheumatoid arthritis. tendonitis, injuries, and osteoarthritis. The therapeutic efficacy of MLX is limited due to its reduced solubility, which results in poor dissolution and minimal absorption from the gastrointestinal tract (GIT) at physiologic pH. The gastrointestinal adverse effects of MLX, which include bleeding, ulceration, dyspepsia, and stomachaches, severely limit its clinical use and may potentially limit long-term use. Therefore, creating an appropriate drug carrier system is essential for the effective and regulated administration of MLX to the colonic area. [5,6]

Controlling the drug release is critical for optimal delivery of the medicine at the site of action after oral administration. A controlled release delivery system has the capability to maintain a consistent plasma drug concentration for an extended period, reducing the adverse effects associated with traditional dose forms. Unfortunately, poor drug solubility, degradation, low bioavailability, and bio-distribution make it difficult to pinpoint the site of action. Encapsulating the drug in a polymeric matrix that allows for precise and controlled drug release at a steady rate for a long period is one strategy to address low solubility and poor bioavailability. [7-11]

The diverse and adaptable properties of polymeric particulate systems, including microparticles, nanoparticles, and microsponges, have recently garnered significant interest. In the meantime, biocompatible and biodegradable polymers are frequently used to make microparticles and nanoparticles, which are then used as drug carriers to overcome issues with low solubility, restricted bioavailability, and drug degradation, as well as to control controlled release distribution at the site of action.

Microparticles with diameters ranging between 1–1000 µm are spherical particles with an active pharmacological ingredient in the core and a polymeric coating that normally controls drug release from the microparticles and can be fabricated by numerous methods such as solvent evaporation, fluidized bed method, conservation method, spray drying, and interfacial polymerization method.

In the present research work, microparticles were fabricated through the oil in oil (O/O) emulsion solvent evaporation (ESE) method, because it is simple to make, does not require harsh processing conditions, and also, does not impact drug activity. It is mostly used to microencapsulate drugs that dissolve

in the dispersion phase and have low aqueous solubility. [12-16]

This method has been used in a wide range of industries, including printing, chemicals, and medicines.9. Microencapsulation serves several purposes: (i) shielding delicate materials from the outside world; (ii) disguising the material's organoleptic qualities (colour, taste, smell); (iii) achieving controlled drug release; (iv) ensuring safe handling of hazardous materials; (v) achieving targeted drug release; and (vi) preventing unfavourable effects such as gastric irritation (aspirin is the first medication used to prevent gastric irritation).10 Therefore, the goal of the current study was to create and evaluate meloxicam-loaded microcapsules for colon-specific drug delivery using pH-dependent polymers.

2. MATERIALS AND METHODS

2.1. Materials

Meloxicam was received as a gift sample from Zydus Lifesciences Ltd, Ahmedabad. The Eudragit RL-100 and RS-100 are obtained from Evonik Industries, Mumbai. Acetone, Span 80, Light liquid paraffin and Heavy liquid paraffin from Karnataka fine chem. Ltd, Bangalore. The other solvents and reagents used were of analytical grade.

2.2. Compatibility Studies

Compatibility of the MLX with polymers viz. Eudragit RL/RS 100, and physical mixture of the main formulation was established by infrared absorption spectral analysis (IR). Any changes in chemical composition of the drug after combining it with the excipients were investigated with I.R. spectral analysis. In the present study, the potassium bromide disc (pellet) method was employed.

2.3. Preparation of microcapsules of MLX

Emulsification-solvent evaporation method

Accurately weighted Eudragit RL-100 and RS-100 were dissolved in 10 ml of acetone to form a homogenous polymer solution. Core material, i.e. MLX was added to the polymer solution and mixed thoroughly. This organic phase was slowly poured at 15^{o}C into liquid paraffin (150 ml) containing 1% w/w of Span-80 with stirring at 1200 rpm to form a smooth emulsion. Thereafter, it was allowed to attain room temperature and stirring was continued until residual acetone evaporated and smooth-walled, rigid and discrete microcapsules were formed. The microcapsules were collected by decantation and the product was washed with petroleum ether (40-60^{o}C), four times and dried at room temperature for 3 hrs. The microcapsules were then stored in a desiccators over fused calcium chloride.

Six batches from F-1 to F-6 were prepared with different proportions of core to coat materials. Where F-1 and F-2 contains the drug with polymers Eudragit RL/RS 100, F-3 and F-4 contains the drug with Eudragit RL100 and F-5 and F-6 contains the drug with Eudragit RS100 (Table1).

Table 1 Formulation Design of MLX Microcapsules.

Sl No	Ingredients	Formulation code					
		F1	F2	F3	F4	F5	F6

1	Drug(mg)	1000	1000	1000	1000	1000	1000
2	Eudragit RL-100 (mg)	300	500	300	500	-	-
3	Eudragit RS-100 (mg)	300	500	-	-	300	500
4	Span-80 (ml)	0.5	0.5	0.5	0.5	0.5	0.5
5	Acetone (ml)	10	10	10	10	10	10

2.4. Evaluation of microcapsules

2.4.1. Particle size and Surface morphology

Determination of average particle size of MLX microcapsules was carried out by optical microscopy in which stage micrometer was employed. A minute quantity of microcapsules was spread on a clean glass slide and average size of 300 microcapsules was determined in each batch.

Scanning Electron Microscopy has been used to determine particle size distribution, surface topography, texture and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large part to simplicity of sample preparation and ease of operation. The studies were carried out by using JEOL JSM T-330 Scanning microscope. Dry microcapsules were placed on an electron microscope brass stub and coated with gold in an ion sputter. Picture of microcapsules were taken by random scanning of the stub.

2.4.2. Frequency distribution analysis

Determination of average particle size of MLX microcapsules was carried out by optical microscopy in which stage micrometer was employed. A minute quantity of microcapsules was spread on a clean glass slide and average size of 300 MLX microcapsules was determined in each batch. In order to be able to define a frequency distribution or compare the characteristics of particles with many different diameters, the frequency distribution can be broken down into different size ranges, which can be presented in the form of a histogram. Histogram presents an interpretation of the frequency distribution and enables the percentage of particles having a given equivalent diameter to be determined.

2.4.3. % Yield and Drug entrapment efficiency

The percent yield of each of the sample was calculated from the expression:

$$\% \text{ Yield} = \frac{weight\ of\ micro\ particles}{weight\ of\ solid\ starting\ materials} \text{ X } 100$$

- **Determination of percentage drug entrapment efficiency (PDE)**

Efficiency of drug entrapment for each batch was calculated in terms of percentage drug entrapment as per the following formula

$$\text{PDE} = \frac{Practical\ drug\ content}{theoretical\ drug\ content} \text{ X } 100$$

- **Drug content:**

In a 100 ml volumetric flask, 25 mg of crushed microcapsules were taken, and volume was made up to mark with pH 7.4. The flask was shaken for 12 hours using an orbital shaker incubator. Then the solution was filtered and from the filtrate appropriate dilutions were made and absorbance was measured at 362 nm.

2.4.4. *In-vitro* dissolution studies

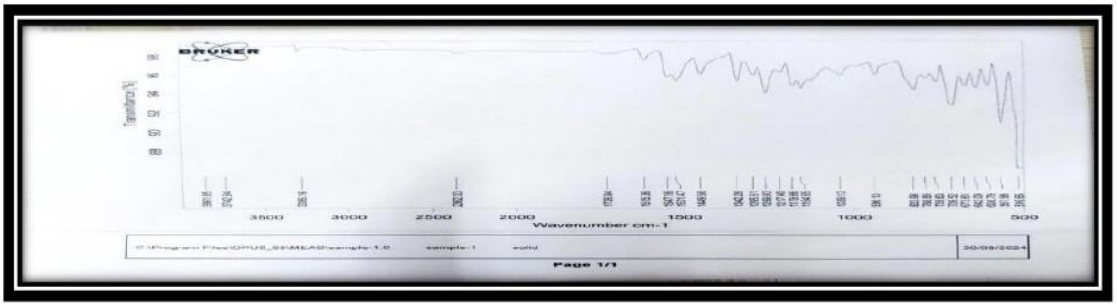
In-vitro dissolution profile of each formulation was determined by employing USP XXIII rotating basket method (900 ml pH 1.2, pH 6.8 and pH 7.4 phosphate buffer, 100 rpm, 37°±0.5°C). Microcapsules of MLX was loaded into the basket of the dissolution apparatus. 5 ml of the sample was withdrawn from the dissolution media at suitable time intervals and the same amount was replaced with fresh buffer. The absorbance of the filtrate was determined at wavelength of 362 nm against blank. The amount of drug present in the filtrate was then determined from the calibration curve and cumulative percent of drug release was calculated.

3. RESULTS AND DISCUSSION

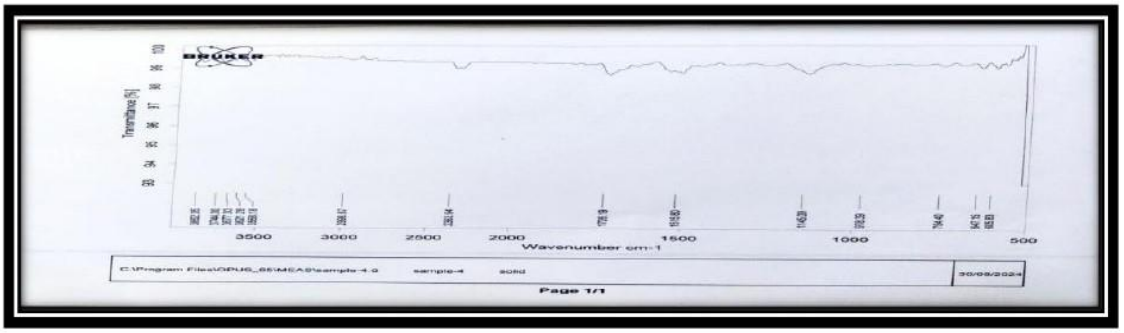
In the present study, an attempt was made to develop and evaluate Eudragit microcapsules of MLX for colon specific delivery and for better treatment of Arthritis. Colonic delivery of MLX could prevent unwanted systemic side effects.

3.1. Compatibility study by IR Spectroscopy

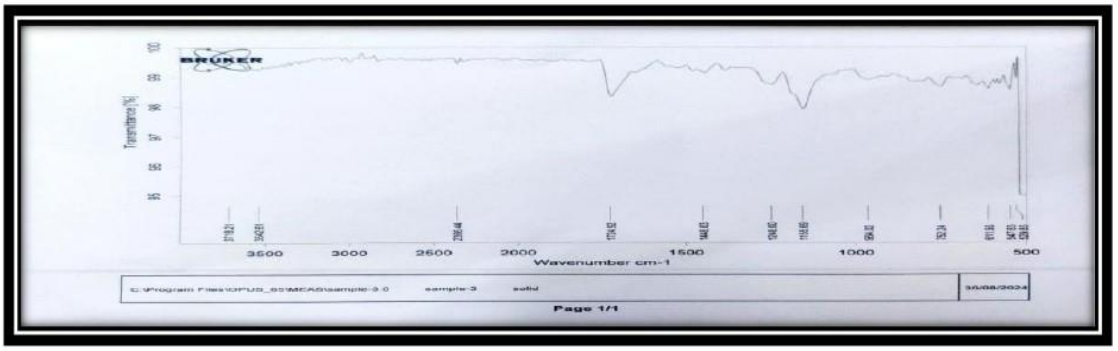
Compatibility study was carried out to check for any possible interaction between the drug and the polymers. From the spectra of MLX, physical mixture of MLX and polymers and MLX microcapsules, it was observed that all characteristic peaks of MLX were present in the combination spectrum thus indicating compatibility of MLX and polymers as shown in Fig 1. The IR studies indicated that there is no drug-polymer incompatibility problem.



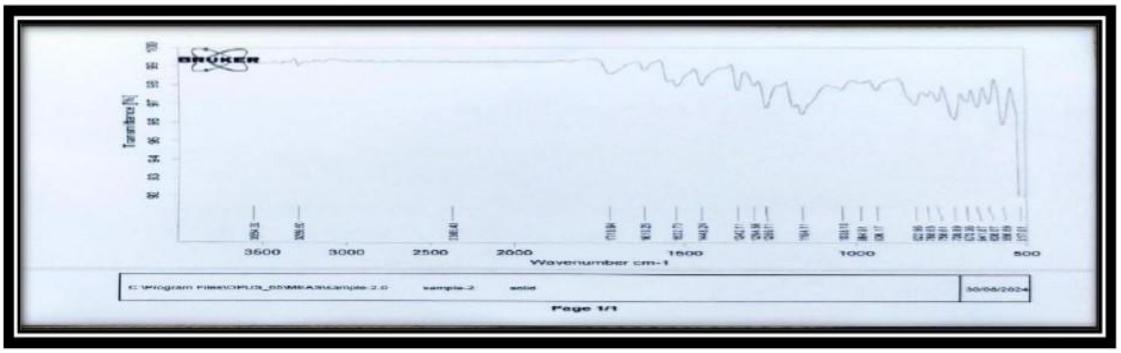
(A)



(B)



(C)



(D)

Fig 1: IR Spectrum of (A) MLX, (B) physical mixture of MLX, Eudragit RL100, (C) physical mixture of MLX, Eudragit RS100 and (D) MLX microcapsules of Eudragit RL/RS100

3.2. Scanning Electron Microscopy (SEM)

Scanning electron microscopy was performed to characterize the surface of the formed microcapsules. Particles are found to be spherical, smooth and discrete. Scanning electron photomicrographs of all the six formulations are shown in Fig 2. Surface smoothness of MLX microcapsules was increased by increasing the polymer concentration.

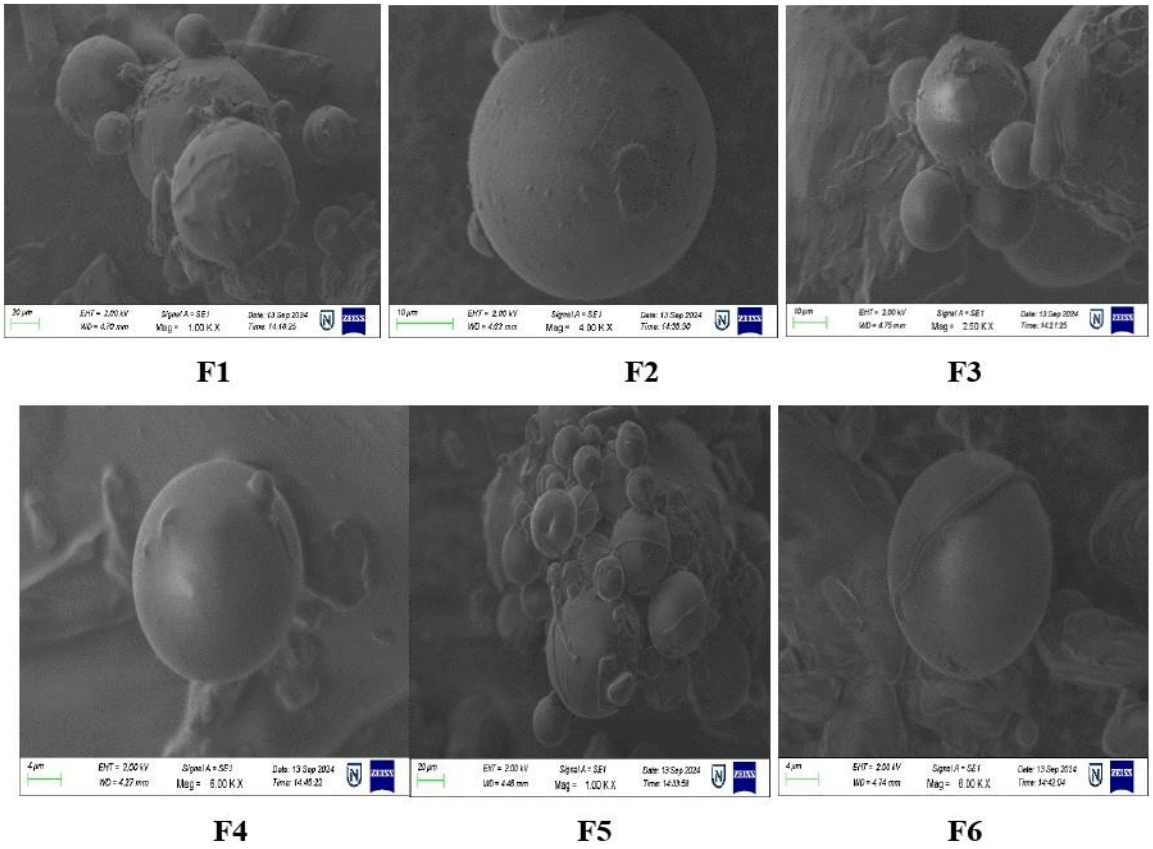


Fig 2: SEM Photography of MLX microcapsules of F1-F6

3.3. Determination of average particle size

The arithmetic mean size of the formulations was determined by the optical microscope, fitted with an ocular micrometer and stage micrometer. The average mean particle sizes of the microcapsules were found to be 628,708, 798, 839, 782 and 870 µm for formulations F-1, F-2, F-3, F-4, F-5 and F-6 respectively (Table 2 and Fig 3).

The mean particle size of the microcapsules significantly increased with increase in polymer concentration and was ranged in between 628 to 870µm. The reason must be, the viscosity of medium increases at a higher polymer concentration resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities. This may be resulting in the formation of larger particles. The significant increase may be because of the increase in the viscosity of the droplets (may be due to the increasing concentration of polymer solution).

Table 2: Average Diameter of MLX Microcapsules

Sl no	Formulation code	Average size (µm)
1	F 1	628 ± 2.73
2	F 2	708 ± 6.53
3	F 3	798 ± 3.83
4	F 4	839 ± 7.06
5	F 5	782 ± 4.02
6	F 6	870 ± 7.00

SD= Standard Deviation (n=3)

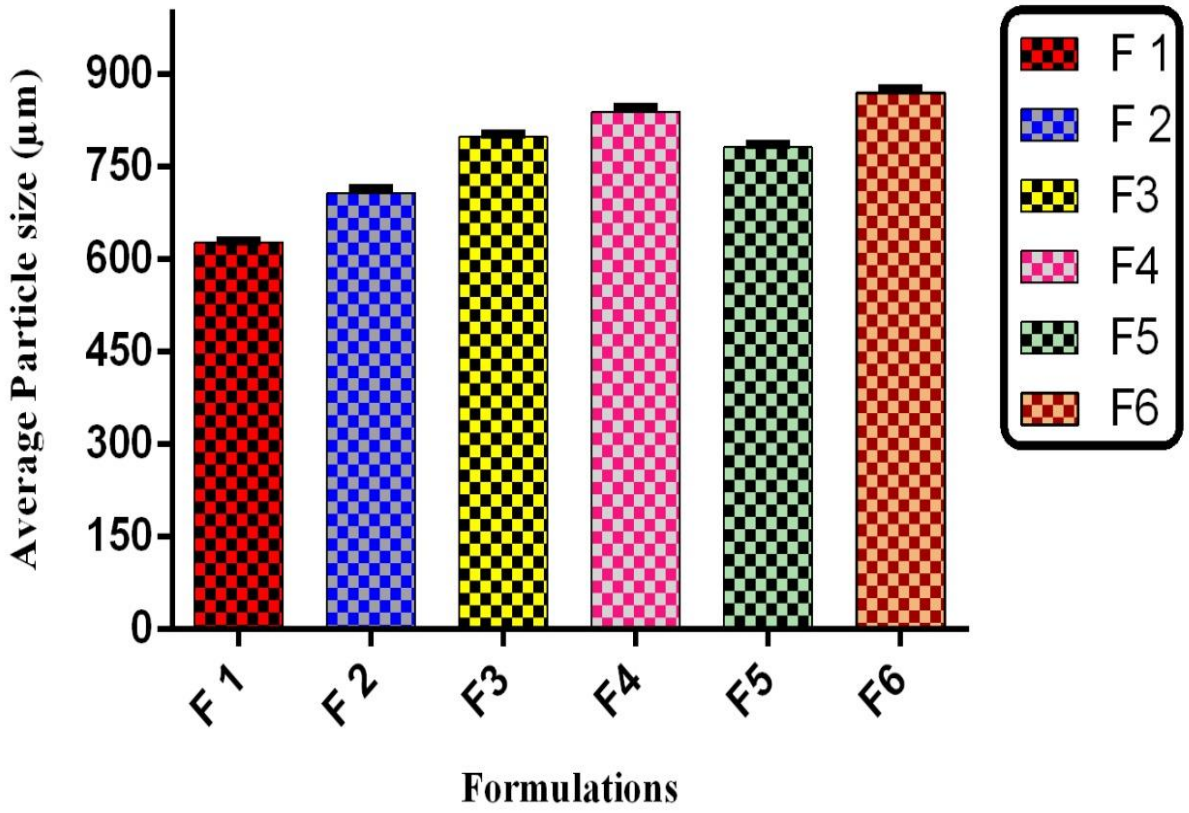


Fig 3: Average Diameter of MLX microcapsules

3.4. Frequency distribution analysis

The results of frequency distribution studies and histograms showed the normal frequency distribution of microcapsules (Table 3 and Fig 4). The mean particle yield for all the formulations was more as shown Table 4. A positive correlation between solid content and percentage yield was observed. This may be explained by the fact that though a constant amount of material is always lost in processing, this loss is proportionately less significant when the solid content is more (e.g. If the loss in processing is 10 mg then it is more significant for a 100 mg sample, but much less significant for a 500 mg sample).

Table 3: Frequency Distribution data of MLX microcapsules

Size range	Number of particles					
	F 1	F 2	F 3	F 4	F 5	F 6
500-550	15	5				
550-600	25	25	15	14		
600-650	25	30	45	30	25	20
650-700	40	40	60	45	60	40
700-750	90	50	95	70	90	85
750-800	65	85	35	65	75	95
800-850	45	65	25	55	50	35
850-900			20	21		25
900-950			5			

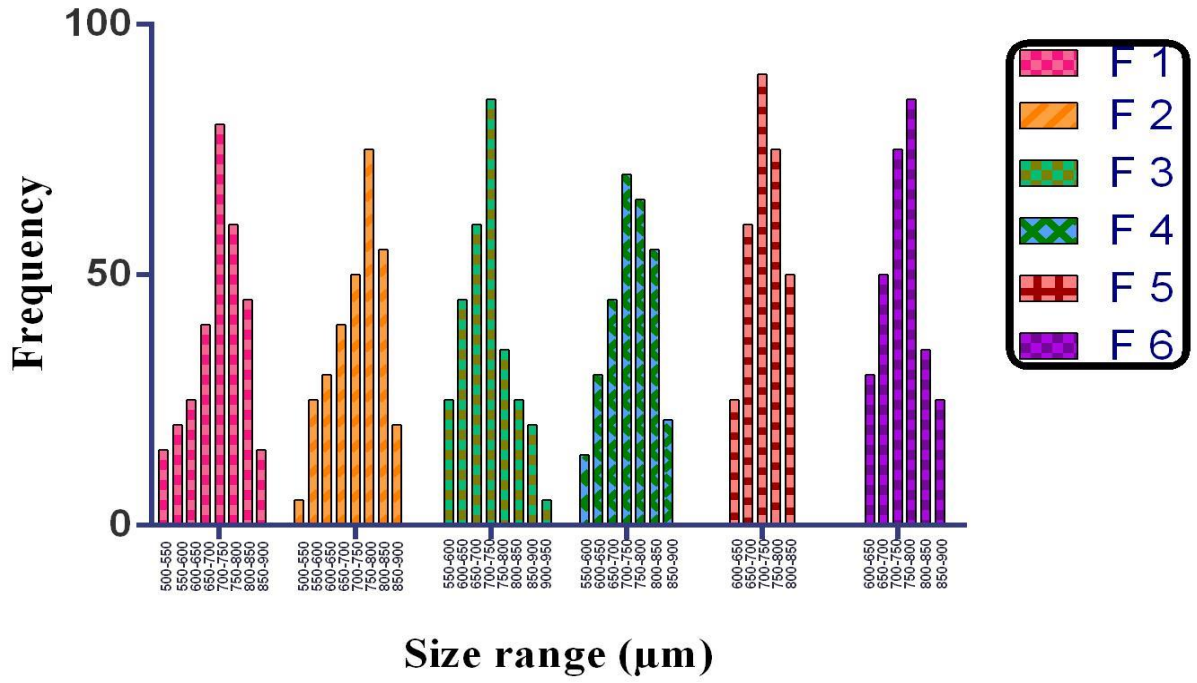


Fig 4: Frequency Distribution of MLX microcapsules

3.5. Drug entrapment efficiency

Entrapment efficiency increase with increase in the polymer concentration from the results it can be inferred that there is a proper distribution MLX in the microcapsules and the deviation is within the acceptable limits. The percentage of the drug content found to be in the range of 20.42% to 82.32%. The percentage entrapment efficiency was found to be 26.00% to 94.50%. The result obtained was given in the Table 4 and Fig 5. A maximum of 94.50%, 86.20% and 73%, drug entrapment efficiency was obtained in the MLX microcapsules. The order of drug entrapment efficiency was found to be F2 >F1, F4>F3 and F6>F5

Table 4: Drug entrapment efficiency of MLX microcapsules

Formulation	% Yield	% Drug Content	Entrapment Efficiency (%)
F1	76.49	69.82	56.60 ± 1.50
F2	96.99	82.32	94.50 ± 1.09
F3	79.10	47.99	67.00 ± 3.50
F4	90.40	70.02	86.20 ± 4.07
F5	50.91	20.42	26.00 ± 2.30
F6	83.86	69.88	73.00 ± 1.05

SD= Standard Deviation (n=3)

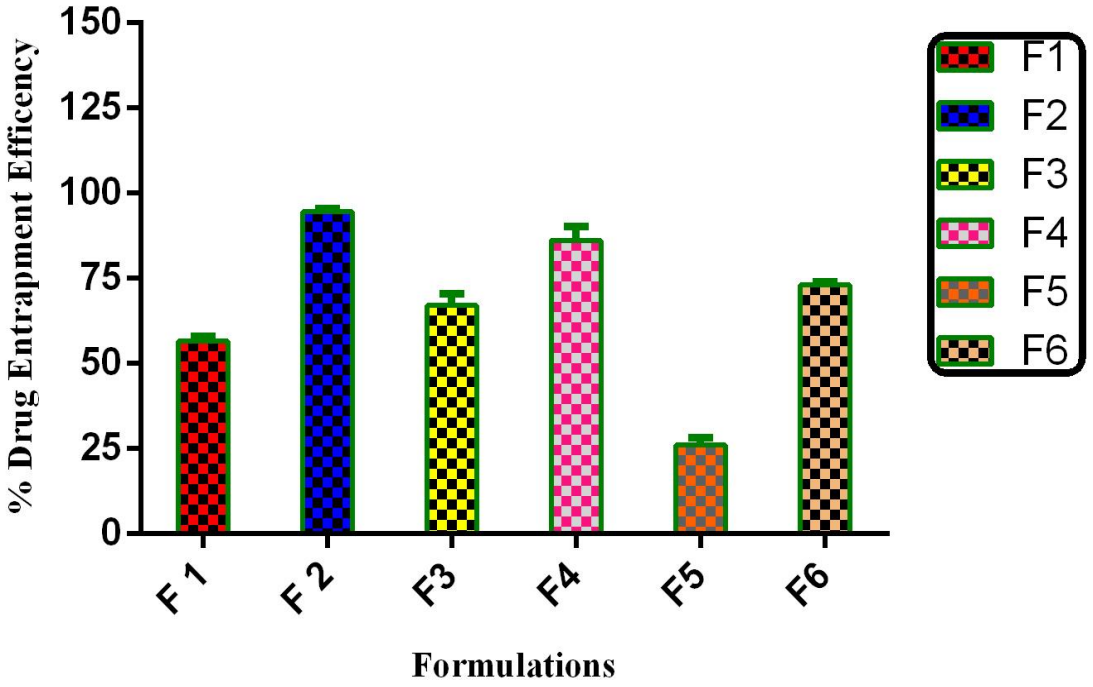


Fig 5: Drug entrapment efficiency of MLX microcapsules

3.6. *In-vitro* release studies of MLX microcapsules

. It was observed that the drug release from the formulations decreased with increase in the amount of polymer added in each formulation. The release showed a bi-phasic release with an initial burst effect. In the first hour drug release was 8.03%, 7.25%, 14.32%, 11.46%, 16.09% and 13.14% for F1 to F6 respectively. The mechanism for the burst release can be attributed to the drug loaded on the microcapsules

or imperfect entrapment of drug. The overall cumulative % release for F1, F2, F3, F4, F5 and F6 were found to be 94.92%, 81.84%, 90.34%, 84.43%, 89.85% and 86.34% at the end of 10th hour (Fig 6).

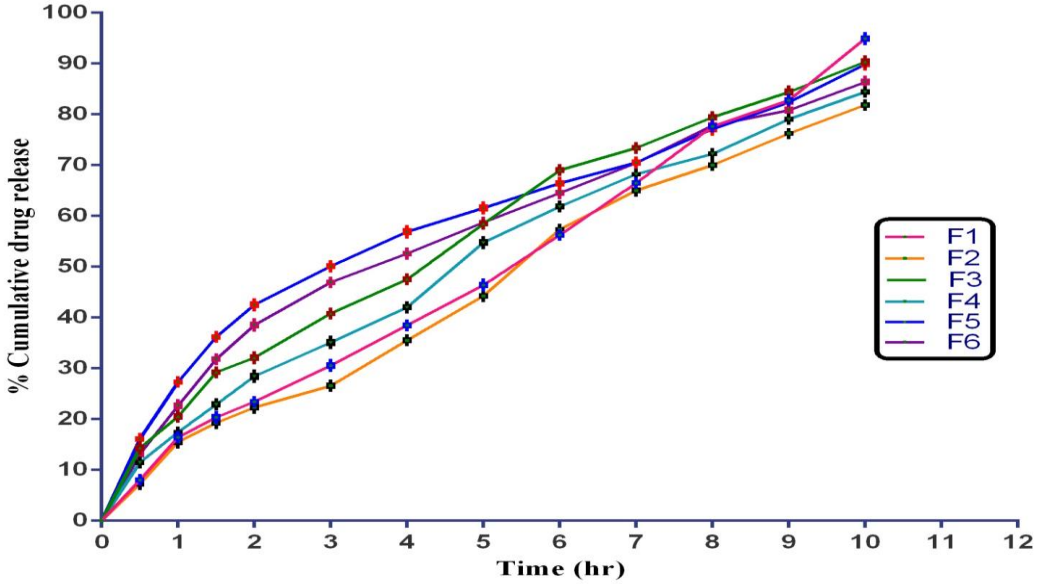


Fig 6: *Invitro* release profile of MLX microcapsules

4. CONCLUSION

From the results it was concluded that the prepared MLX microcapsules can be considered as one of the promising formulation techniques for preparing colon specific drug delivery systems for the treatment of Arthritis.

REFERENCES

1. Ci Navarro-Ruíz E, Álvarez-Álvarez C, Peña, M.Á, Torrado-Salmerón, C, Dahma, Z,de la Torre-Iglesias, P.M. Multiparticulate Systems of Meloxicam for Colonic Administration in Cancer or Autoimmune Diseases. Pharmaceutics. 2022; 14: 1504.
2. Alka Singh, Shalu Verma, Tarun Parashar, Kiran Dobhal, Gauree Kukreti. Formulation and Evaluation of Microspheres as an effective Colon Targeting Drug Delivery System. Research J. Pharm. and Tech. 2023; 16(4):1919-24.
3. Cheng G, Jou MJ, Sun J, Hao XU, He YX. Time- and pH dependent colon-specific drug delivery for orally administered diclofenac sodium and 5-amino salicylic acid. World J Gastroenterol. 2004;10(12):1769-74.
4. Abdul B, Bloor J. Perspectives on colonic drug delivery, business briefing. Pharm Tech. 2003:185-90.
5. Nagai N, Ogata F, Otake H, Kawasaki NJ. Oral administration system based on meloxicam nanocrystals: decreased dose due to high bioavailability attenuates risk of gastrointestinal side

effects. Pharmaceutics. 2020;12(4):313.

6. Gómez-Gaete C, Retamal M, Chávez C, Bustos P, Godoy R, Torres-Vergara P. Development, characterization and in vitro evaluation of biodegradable rhein-loaded microparticles for treatment of osteoarthritis. Eur J Pharm Sci. 2017;96:390–7.
7. Maqbool I, Akhtar M, Ahmad R, Sadaquat H, Noreen S, Batool A, et al. Novel multiparticulate pH triggered delayed release chronotherapeutic drug delivery of celecoxib-β-cyclodextrin inclusion complexes by using Box-Behnken design. Eur J Pharm Sci. 2020;146:105254.
8. Meng F, Wang S, Wang Y, Liu H, Huo X, Ma H, et al. Microencapsulation of oxalic acid via oil-in-oil (O/O) emulsion solvent evaporation. Powder technology. 2017;320:405–11.
9. Dubey R, Shami TC, Bhasker Rao KU. Microencapsulation technology and applications. Def Sci J. 2009;59(1):82–95.
10. Jyothi NVN, Prasanna PM, Sakarkar SN, Prabha KS, Ramaiah PS, Srawan GY. Microencapsulation techniques, factors influencing encapsulation efficiency. J Microencapsul. 2010;27(3):187–97.
11. Wasay SA, Jan SU, Akhtar M, Noreen S, Gul R (2022) Developed meloxicam loaded microparticles for colon targeted delivery: Statistical optimization, physicochemical characterization, and in-vivo toxicity study. PLoS ONE 17(4): e0267306.
12. Yegireddy M, Nadoor P. Rao S, Hanumanthu P B. Rajashekaraiah R, Ramachandrappa S C et al. Chitosan Encapsulated Meloxicam Nanoparticles for Sustained Drug Delivery Applications: Preparation, Characterization, and Pharmacokinetics in Wistar Rats. Molecules. 2022; 27: 7312.
13. Nijamuddin M, Ahmed VPA, Shelar S, Khan T. Preparation and evaluation of Flurbiprofen microcapsule for colonic drug delivery system. Int J of Pharm and Pharma Sci 2010;2:83-7.
14. Bussermer T, Bodmeier R. Formulation parameters affecting the performance of coated gelatin capsules with pulsatile release profile. Int J Pharm 2003;267:59-68.
15. Lemmer B. Chronopharmaco kinetics; implication for drug treatment. J Pharm Pharmacol 1999;51:887-90.
16. Gang Cheng, Feng A, Mei-Juan Zou, Jin Sun, et al. Time and pH-dependent colon-specific drug delivery for orally administered diclofenac sodium and 5-amino salicylic acid. World J Gastroenterol 2004;10(12):1769-7