Section A-Research paper

Formulation and *In-Vitro* Evaluation of Sustained Release Matrix Tablet Containing Methocarbamol as Promising Skeletal Muscle Relaxant

Vishwas C. Bhagat[1]*, Pravin B. Awate[1], Dipak P. Kardile[1], Onkar P.Pawar[1], Rajkumar V. Shete[1] ,Sukanya R. Mane [2], Gaurav V. Kharat [2], Rushikesh P. Wagh[3], Samiksha S. Upadhye[3], Aishwarya T. Jadhav[3]

[1]*Department of Pharmaceutics, Rajgad Dnyanpeeth's College of Pharmacy, Bhor, Tal. Bhor Dist. Pune 412206 (Maharashtra), India.*
[2]*Department of Quality Assurance Techniques, Satara College of Pharmacy, Satara 415001(Maharashtra), India*
[3]*Department of Pharmaceutics, Dakshin Solapur Taluka Shikshan Mandal's College of Pharmacy, Solapur, Tal. Dakshin Solapur Dist. Solapur 413004 (Maharashtra), India.*

*(*Corresponding author: Dr. Vishwas C. Bhagat. Assistant Professor, Rajgad Dnyanpeeth's College of Pharmacy, Bhor, Email ID: vishumed@gmail.com,Onkarpawarop96@gmail.com, Tel: + 91-9860631141)*

Abstract

The present research work aim was to formulate a sustained release matrix tablet containing Methocarbamol, which is used in the treatment of acute musculoskeletal pain. Sustained release matrix tablet containing methocarbamol was prepared by using the direct compression method. Methocarbamol is having short half life. Sustained release matrix tablet prepared by using Design-Expert version13 software with central composite factorial designs in which drug retardant polymer HPMC K100M and binder like xanthan gum are used in different concentrations.

The formulated batches of tablets were evaluated for hardness test, weight variation test, friability test, drug content, and *in vitro* % drug release. The characterization of the tablet shows satisfactory results of a tablet like weight variation and thickness. The formulation F4 showed the highest amount of drug content. FTIR and DSC studies reveal that there are no interactions between drug and excipients that mean drugs and excipients are compatible with each other. Formulation F4 is optimized batch, passes evaluation parameters and maximum % drug release i.e. 100.14 % upto12 hrs. Therefore, the sustained release matrix tablet is an effective approach for avoiding daily multiple doses and for better patient compliance.

Keywords: Methocarbamol, HPMC K100M, Xanthan Gum, Matrix tablet,Sustained release drug delivery.

Introduction[1,2,3,4]

Oral drug delivery is most common and practical method of drug delivery is via the oral route. The oral mode of administration has drawn more attention in the pharmaceutical industry than designing medication delivery in multiple ways due to the greater versatility in dosage form design. The majority of orally delivered medications are designed to permeate the general circulation and perfuse to different bodily tissues; targeting is not a key problem in most cases. As a result, sustained-release devices are commonly used. The premise is that enhancing the concentration at the absorption site will lead to higher levels of the drug in the bloodstream, thereby increasing the concentration of the drug at the intended site of action. Matrix-based approaches are extensively employed for

achieving sustained release of drugs. The release system in these methods controls and delays the dispersed or dissolved release of the drug. The term "matrix" actually refers to a thoroughly combined mixture of one or more medications and a gelling agent, such as hydrophilic polymers. Muscle spasticity is a common feature observed in various clinical conditions such as trauma, myositis, muscular and ligamentous sprains and strains, intervertebral disc disease, tetanus, strychnine poisoning, neurologic disorders, and exertional rhabdomyolysis. This increased spasticity is attributed to heightened tonic stretch reflexes, resulting in motor neuron hyperexcitability in the spinal cord. These reflexes are modulated by descending pathways within the central nervous system (CNS). Methocarbamol is a centrally-acting muscle relaxant that shares chemical similarities with guaifenesin. The precise mechanism of its action is not fully understood, as it does not directly relax the striated muscle, nerve fibers, or motor endplate. Furthermore, it possesses sedative properties. Methocarbamol is frequently prescribed as an additional treatment for acute inflammatory and traumatic skeletal muscle disorders.

Materials and Methods

Methocarbamol was obtained fromSynthokem Labs Pvt. Ltd., Hyderabad.HPMC K100M, Xanthan Gum, Magnesium Stearate, Microcrystalline cellulose and Talc were procured from SD Fine chemicals Ltd., Mumbai.

Determination of absorption maxima[5,6]

A solution of containing the concentration 10 µg/ml was prepared in 0.1 N HCl, phosphate buffer of pH 6.8, respectively, ultraviolet (UV) spectrum was taken using Double beam UV/visible spectrophotometer. The solution was subjected to scanning within the wavelength range of 200-400 nm.

Drug-excipients compatibility study by FTIR spectroscopy [7,8]

In order to assess potential drug-excipient interaction, a technique known as infrared spectra matching was employed. A combination of the drug and excipients was prepared and mixed together in a physical mixture, utilizing a 1:1 ratio. An adequate quantity of potassium bromide was added during the blending process. A transparent pellet was formed using a hydraulic pressurized at 10 tons pressure from approximately 100 mg of this blended mixture was used.. It was scanned using a SHIMADZU FTIR Spectrophotometer from 4000-400cm-1. In order to identify any peak appearance or disappearance, the IR spectra of the physical combination was contrasted with that of the excipients and the pure drug.

Differential Scanning Spectroscopy [9,10]

To reverse the effects of oxidation and pyrolysis, samples of the medication were hermetically packed in flat-bottomed aluminium pans and heated in the DSC-60 (Shimadzu, Kyoto, Japan) in a nitrogen environment. The temperature range was 50-120°C, and the rate of heating was 10°C/min. The DSC thermograms were recorded subsequently, the mixture was compared to the standard.

Experimental Design [11,12,13]

Based on initial exploratory studies, the two most significant independent formulation factors that influence cumulative release in the initial hour and drug release rate over a 12-hour period are xanthan gum (X1) and HPMC (X2).Thus 'central composite design' (CCD) with α =1 was employed and studied at 3 levels eachwith the aid of the software Design-Expert® (Version 13, Stat-Ease Inc., USA), the trial design was completed in order to optimize the factors with respect to the response variables.In CCD the face centered design (CCF) was chosen as to detect any non-linearity in factor-response relationship. According to the face centered central compositedesign the 9 experimental runs of the CCD matrix were carried out.

Table 1: Independent Variables and their values (α = 1)

Independent variable	**Low level (-1)**	**Intermediate Level (0)**	**High level (+1)**
(X1) Xanthan gum	50 mg	100 mg	150 mg
(X2) HPMC K100M	50 mg	100mg	150 mg

Table 2: Formulation Table

Batch	**Methocarbamol**	**Xanthan Gum** (Coded values)	**HPMC K100M** (Coded values)	**MCC**	**Mg. Stearate**	**Talc**	**Total Weight**
1	500	0	-1	330	10	10	1000
2	500	+1	+1	180	10	10	1000
3	500	+1	-1	280	10	10	1000
4	500	0	+1	230	10	10	1000
5	500	-1	0	330	10	10	1000
6	500	0	0	280	10	10	1000
7	500	-1	+1	280	10	10	1000
8	500	-1	-1	380	10	10	1000
9	500	+1	0	230	10	10	1000

all values are expressed in mg

Method of preparation[14,15]

Formulation steps for matrix tablets using direct compression method.

Sieving: The active ingredient was then passed through sieve #60 and then same sieve was used to separate out other ingredients.

Dry mixing: To ensure uniform mixing of the ingredients with the drug, all the components (including the active ingredient) placed in a poly bag and mixed for 5 minutes.

Lubrication: Talc was mixed uniformly with the powder blend in a poly bag for five minutes.

Compression: Subsequently, the powder blend was compacted into tablets weighing 1000mg. each using 16 mm oval-shaped punches in single-rotary tablet compression machines.

Evaluation of sustained release matrix release tablet

Pre-compression parameters[16,17]

Angle of repose:

By using the funnel technique, the angle of repose of the powdered mixture was determined. The funnel was filled with the carefully blended powder mixtures. The funnel's height was adjusted so that its point slightly touched the top of the mixture's apex, allowing the powder to flow freely through the funnel and onto the surface. We measured the diameter of the powder coneand the following formula was used to determine the angle of repose.

$$\tan\theta = h / r$$

h = height in cm

r = radius in cm

θ = Angle of repose

Bulk Density:

It is the proportion of the powder's overall weight to its bulk volume. The weighted powder, which (passed through a standard sieve #60), was poured into a measuring cylinder, and the initial volume—which is bulk volume—was noted. The provided formula is utilized for calculating the bulk density.

$$\mathbf{Bulkdensity = Massofpowder / Bulkvolume}$$

Tapped density:

It's the ratio of powder's total bulk to its tapped volume. The powder was tapped 50-100 times to determine its quantity. It is formulated in the following way.

$$\mathbf{Tappeddensity = Massofpowder / Tappedvolume}$$

Hausner's ratio:

It is the ratio of tapped density to bulk density.

$$\mathbf{Hausner' ratio = tappeddensity / bulkdensity}$$

Carr's index:

This straightforward test may be used to estimate the mass and tapped densities of a powder as well as the pace at which it packed down. It is described in the formula below.

$$\mathbf{Carr'sindex} = [(\mathbf{Tappeddensity} - \mathbf{Bulkdensity})\mathbf{100}]/\mathbf{tappeddensity}$$

Post Compression Parameters[16,17]

Weight Variation Test:

To assess weight variation, 10 tablets from each formulation were measured using an electronic balance (F1 to F9). Subsequently, the average weight was calculated. Only two of the individual weights for the 1000 mg tablets differed from the average weight by over 5 percent, and none exceeded that percentage.

Hardness test:

The tablet's ability to withstand mechanical shocks during usage was evaluated through hardness testing. The Monsanto hardness tester was employed to measure the tablets' hardness. It is measured in kilograms per square centimeter. Ten tablets are chosen at random and their hardness is determined.

Thickness test :

The thicknesses of the tablets can be measured with a Vernier calliper. The average value is determined using five tablets. The tablet eventually broke when the piston was turned by a threaded screw against a spring. A pointer moves along a gauge in the tube to show the power as the spring is pressed. Tablet variation may pose issues with counting and packaging. Tablet thickness should be kept within 5% of the normal value.

Friability test:

The apparatus was filled with 20 previously measured tablets and given 100 rotations before the tablets were reweighed. The percentage of friability was measured using the following technique.

$$\%\text{Friability} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \text{x } 100$$

Drug content:

Five tablets were chosen at random from each batch, thoroughly crushed, and a powder containing 500 mg of the drug methocarbamol was quantified and diluted in 100ml of a solution containing phosphate buffer at pH 6.8. The mixture was stirred up vigorously. To remove the insoluble substance, Whatman No. 41 filter paper was used in filtration. After that, the dilutions were repeated. The absorbance of the solutions was measured at 274 nm. The drug's content was determined by employing the methocarbamol standard calibration curve in a phosphate buffer solution with a pH of 6.8.

***In-vitro* drug release study** [18,19]

The in vitro dissolving study must be carried out using a USP type II apparatus (paddle type) (Labindia) [Tablet dissolution tester] at 50 rpm. The primary dissolution medium is phosphate buffer pH 6.8, 900 ml, which must be maintained at 37 ±0.5 °C. At a fixed time of every sixty minutes, a sample of the dissolution medium (5 ml) must be removed and then subjected to a filtration process. By detecting the sample's absorbance, a UV

A spectrophotometer from Shimadzu, Japan, was utilized to calculate the amount in which the drug was dissolved. Each batch performed three trials, and the average percent drug release with standard deviation was determined and recorded.

Dissolution apparatus : Type II USP (paddle type)

Dissolution medium: 6.8 PH Phosphate Buffer

Volume : 900 ml

Temperature : 37◦C±0.5◦C

Rpm : 50 rpm

Total dissolution time: 12 Hrs.

Sampling time : 1,2,3,4,5,6,7,8,9,10, 11 & 12 Hrs.

Sampling volume: 5 ml .

Analysis at: UV determinations at 274 nm.

Kinetics of *In vitro* drug release [16]

To investigate the manner of medicine release from tablets, the discharge data was broken down with the accompanying numerical models:

Zero order kinetics

($Q = K_0 t$)

It represents a system in which Drug release frequency is independent of concentration. C is the total amount of drug released in time t, and K_0 denotes the zero order release constant.

First order kinetics

$\text{Log } Ct = \log C_0 - K_{1t}/2.303$

This description pertains to drug release frequency from systems in which the release frequency is influenced by concentration. C_t denotes the quantity of drug released at time t, C_0 represents the initial drug concentration, and K_1 represents the first-order release constant.

Higuchi kinetics

$W = K_2 t^{1/2}$

It refers to drug release from systems in which the solid drug is disseminated in an insoluble matrix and Direct correlation exists between the rate of drug release and the rate of drug diffusion.W is the total amount of medication released during time t, and K_2 is the Higuchi dissolving constant.

Hixson Crowell kinetics.

$(100 - W)^{1/3} = 100^{1/3} - K_3 t$

This concept elucidates the release mechanism in systems where it relies on the alteration of tablet surface area and diameter over time. It primarily applies to systems that degrade or deteriorate over time. K_3 is the release constant, and W is the total amount of medication dissolved at time t.

Korsmeyer and Peppas equation

$\mathbf{M_t / M\infty = K_4 t^n}$

The subsequent equation signifies the drug release from the polymeric system when the release mechanism deviates from Fickian diffusion. F is the total quantity of medication dissolved at time t, K4 is the release constant, and n is the exponent dictating the drug release mechanism. The medication is released from matrix tablets by Fickian diffusion if the release exponent n is equal to 0.45. The release exponent, however, indicates non-Fickian or anomalous diffusion if it is between 0.45 and 0.89.

Stability Studies [18]

ThestabilitystudieswerecarriedoutaccordingtoICHtoassessthedrugformulation stability. Optimized F4 formulation was sealed in Aluminum packinglaminatedwithpolyethylene.Samples werekeptat40°Cand75%RHfor3months. At the end of study period, the formulation was observed for change inphysicalappearance, color,drugcontent,and drugreleasecharacteristics.

Result and Discussion

Determination of wavelength (λ max) of Methocarbamol:

The UV spectrophotometer was utilized to identify the highest wavelength of Methocarbamol in a pH 6.8 phosphate buffer, which was determined to be 274 nm. Wavelength maximum (λ max) of Methocarbamol was observed 274 nm

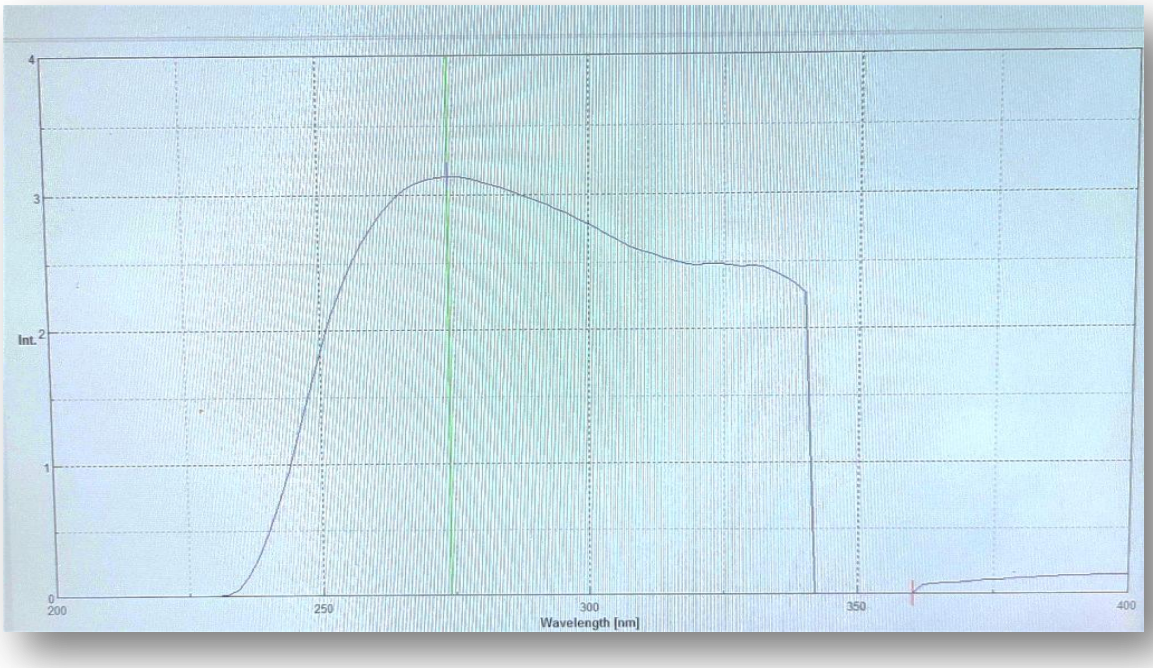

Fig 1:UV spectrum of Methocarbamol

Drug polymer compatibility study byFTIRsspectroscopy:

Methocarbamol FTIR spectra, along with of Xanthan Gum, HPMC K100M , and the drug and polymer mixture do not show any substantial interaction between the two compounds. Fig.2 shows the FTIR spectra of Methocarbamol, Xanthan Gum, HPMC K100M .

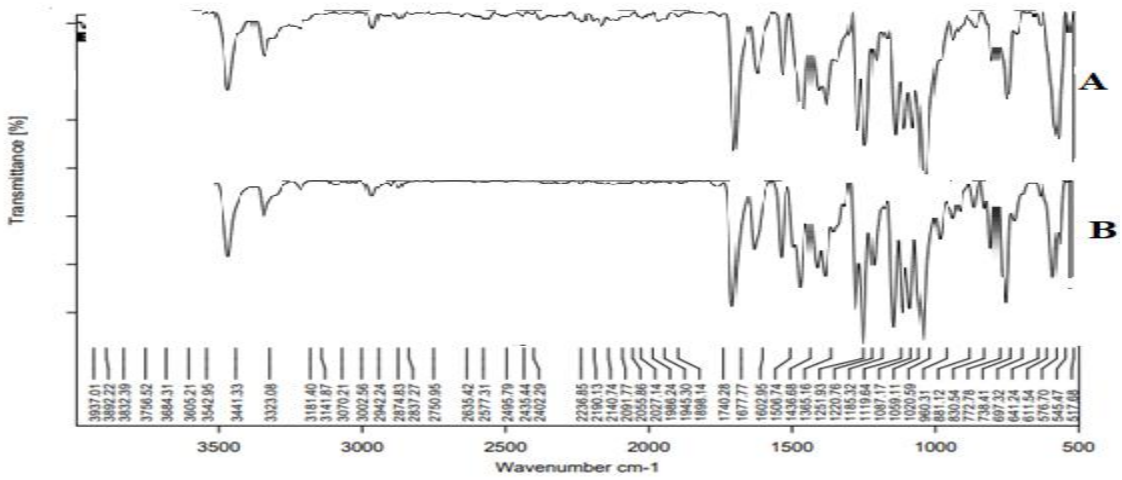

Fig. 2: FTIR spectra of (A): Pure Methocarbamol; (B): Methocarbamol + HPMC K100M+ Xanthan gum

InterpretationofFTIRSpectrum:

Major functional groups present in methocarbamol shows characteristic peaks inFTIR spectrum. Above Fig.2 shows peaks observed at different wave numbers and thefunctionalgroupassociatedwiththesepeaks.Themajorpeaksareidenticalto functionalgroupofmethocarbamol.Hence,the API sample wasconfirmedasmethocarbamol.

Differential Scanning Calorimetry

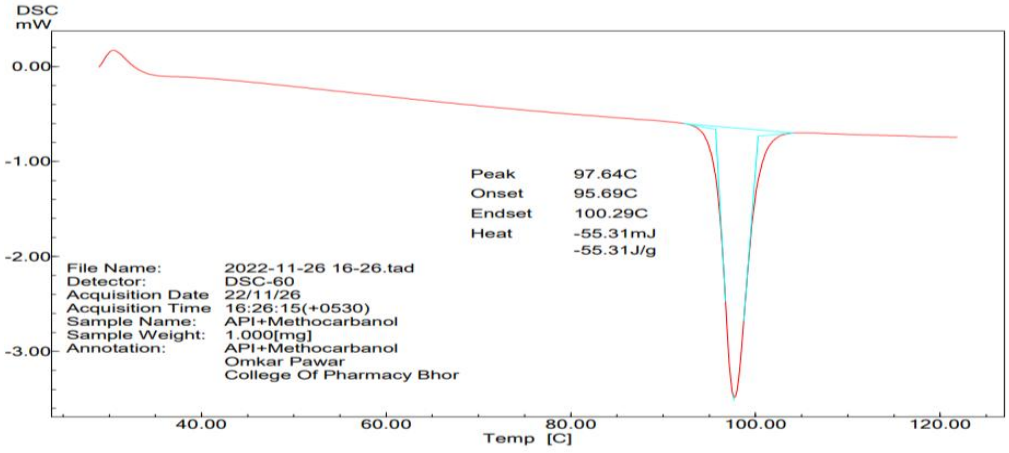

Fig 3: Thermal spectra of Methocarbamol

The analysis was performed on Shimadzu DSC-60 instrument. The peak point was observed at 97.64 ^{0}C with onset point at 95.69 ^{0}C. The steady rate of heating was kept at 10 ^{0}C per min.From DSC analysis , obtained peak value is compared with std peak value and Based on the data, it is fair to infer that the specified API is pure.

Flow properties:

Methocarbamol sustained release drug powder components and other excipients were tested for flow characteristics including, tapped density, bulk density, angle of repose, carr's index, and Hausner's ratio before making the tablets. Table 3 displays the satisfactory results obtained.

Table 3: Evaluation of Flow properties of powder (For Mean ±SDn = 3.)

Batch	Angle of Repose $^{(0)}$	Bulk density (gm/ml)	Tapped density(gm/ml)	Carr's index (%)	Hausner's ratio
1	27.28±0.24	0.57±0.00	0.64±0.00	11.08±0.44	1.12±0.00
2	27.82±0.15	0.52±0.00	0.57±0.00	8.36±0.51	1.08±0.00
3	27.01±0.16	0.57±0.00	0.60±0.00	5.25±0.47	1.06±0.01
4	28.04±0.31	0.549±0.00	0.604±0.00	8.96±0.20	1.11±0.00
5	27.22±0.46	0.531±0.00	0.580±0.00	8.33±0.23	1.09±0.00
6	26.25±0.30	0.528±0.00	0.574±0.00	7.93±0.15	1.08±0.00
7	25.78±0.40	0.519±0.00	0.583±0.00	10.93±0.05	1.12±0.00
8	28.36±0.31	0.551±0.00	0.608±0.00	9.38±0.19	1.10±0.00
9	29.93±0.43	0.517±0.00	0.564±0.00	8.8±0.00	1.09±0.00

Angle of repose:

Every figured group's point of rest was discovered to be between 25.78 and 29.93 exhibiting excellent free flowing properties.

Bulk density and Tapped density

The estimated bulk densities & tapped densities for each individual detailed group were found to range between 0.517 to 0.57 and 0.564 to 0.64 respectively, and are thus within the acceptable limits. The highest possible mass and tap densities, which exhibit excellent pressure properties, were discovered.

Carr's Index

The estimations of rate compressibility go from 5.25 to 11.08 demonstrating that the mixes have great compressibility.

Hausner's ratio

This property was additionally dictated by estimating the Hausner's proportion. Estimations of Hausner's proportion were found between 1.06 to 1.12 individually showing great flow properties.

Post Compression Parameters

Table 4: Post Compression Parameters (±SD *n=3, **n=10)

Batch No. / Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness (mm) ±SD**	3.45±0.04	3.49±0.15	3.56±0.20	3.75±0.17	3.63±0.24	3.60±0.30	3.49±0.19	3.63±0.25	3.64±0.25
Hardness (Kg/cm^2) ±SD*	6.36±0.05	6.36±0.15	6.10±0.15	6.66±0.05	6.86±0.05	7.76±0.05	6.93±0.25	5.56±0.35	7.1±0.20
% Friability (%)±SD*	0.75±0.01	0.75±0.02	0.46±0.05	0.53±0.05	0.73±0.02	0.59±0.12	0.68±0.16	0.43±0.37	0.78±0.07
Weight variation (mg) ±SD*	1001.6±0.57	1001±1.00	1003.3±1.15	1001.3±0.57	1001.6±1.52	1002.6±0.57	1002.3±1.24	1000±0.81	1002±0.47
Drug content (%)±SD*	98.08±0.024	98.26±0.42	98.84±0.48	98.93±0.63	98.27±0.32	97.91±0.54	97.08±0.62	96.75±0.17	96.68±0.82

Thickness test:

Each batch's tablet Thickness varied from 3.45 to 3.75 mm.

Hardness test:

Each batch's tablet hardness varied from 5.56 to 7.76 kg/cm^2.

Weight variation test:

The percentage variations in weight for table 4.presents all the formulas used. Since the percentage of weight variations was less than 5% of the weight, all of the formulated (F1 to F9) tablets passed the weight variation test. All of the tablets had consistent weights and acceptable standard deviation readings.

Friability:

All formulations had a percentage of friability that was less than 1%, ensuring the the tablets' mechanical strength.

Drug content:

In all the nine definitions, the qualities for medication content were observed to be uniform among various clumps of the supported discharge network tablet and ran between 97.08± 0.62 % and 98.93 ± 0.63 %. These qualities are discovered palatable, which guarantees measurements consistency and meets with the necessities of IP (85 to 115 %) of the normal substance.

***In-vitro* drug release study:**

Methocarbamol 'sustained release matrix tablets' were subjected to *in-vitro* drug release tests using phosphate buffer pH 6.8 as the dissolution media. All formulations (F1 to F9) underwent *in-vitro* dissolution studies.The percentage of drug release for formulations F1 to F9 ranged from 0.76% to 100.14 % during the course of 1 to 12 hours. Among these formulations, F4 exhibited the highest percentage of drug release, reaching 100.14% over a 12-hour period. The percentage of drug release increased as the combined concentration of Xanthan Gum and HPMC K100M increased, as indicated by the aforementioned studies. Notably, formulation F4 demonstrated the most favourable*in-vitro* drug release among all the tested formulations.

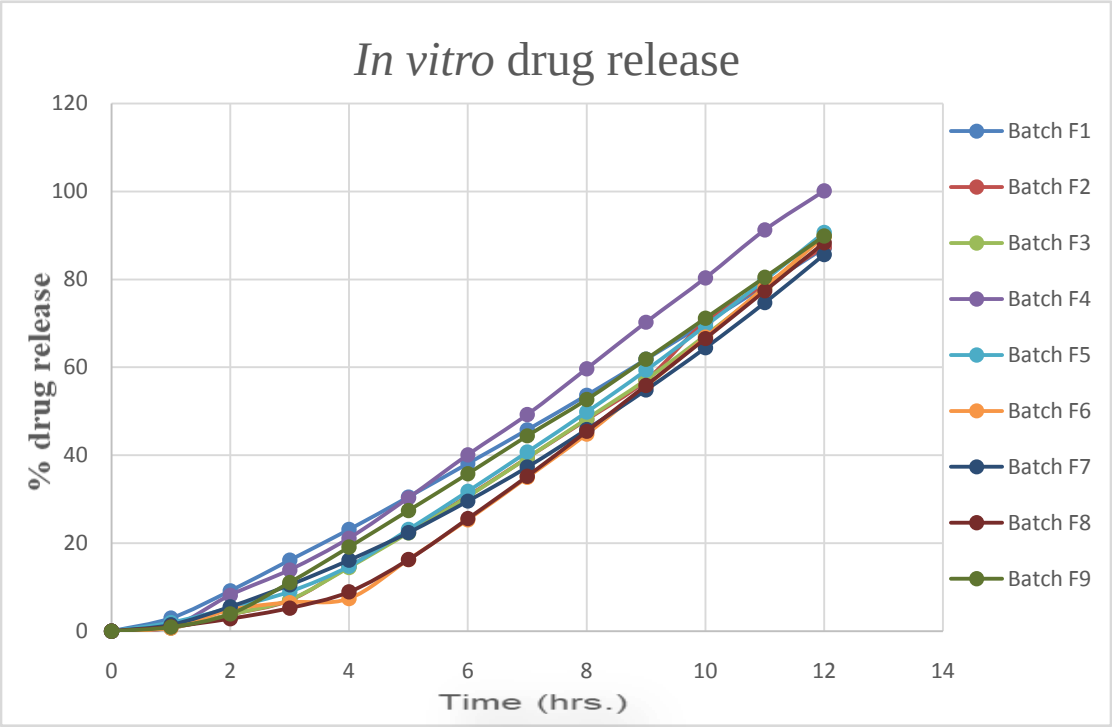

Fig.4 : In-Vitro Drug Release of Prepared Tablet (Batch F1 To F9)

Release Kinetics of In-vitro Drug Release

The in-vitro drug release kinetics were calculated by fitting the data to several kinetic models such as zero order, first order, Peppas- Korsmeyer, Higuchi and Hixson Crowell. The result obtained were represented in table 5

Table 5: *In-vitro* Drug release Kinetics

Mathematical Models (kinetics)					
Sr.no	**Zero-order**	**First order**	**Higuchi**	**Korsmeyer Peppas**	**Hixson Crowell**
	R^2	**R^2**	**R^2**	**R^2**	**R^2**
F1	0.9938	0.9077	0.9627	0.9955	0.9938
F2	0.9839	0.8758	0.9242	0.9936	0.9839
F3	0.9826	0.8351	0.9209	0.9940	0.9826
F4	0.9803	0.7799	0.9162	0.9967	0.9803
F5	0.9826	0.8409	0.9207	0.9966	0.9826
F6	0.9584	0.8165	0.8785	0.9818	0.9584
F7	0.9825	0.8639	0.9216	0.9964	0.9825
F8	0.9651	0.8379	0.8884	0.9922	0.9651
F9	0.9951	0.8799	0.9513	0.9848	0.9951

From the data, the sustained release matrix tablets of methocarbamol formulations showed well-fitted Korsmeyer Peppas kinetics and formulation F4 was shown best among the formulations prepared based on percentage yield, percentage entrapment and in-vitro drug released profiles and also well-fitted the Korsmeyer Peppas kinetics.

Stability study:

Over the course of a three-month period, stability tests for this product's F4 batch conducted in accordance with ICH standards. Studies on stability were done for formulation F4, optimized formulation. There is no physical change, but friability, hardness, and assay have all slightly changed. The optimized batch's dissolution profile was calculated and It turned out that there was a slight decline in the percentage of drug released.

Table 6: Stability studies of batch F4

Sr. No.	**Parameter**	**Stability conditions at**
		40 ^{0}C 75% RH
1	Physical appearance	No change
2	Friability	0.51%
3	Hardness	6.6 kg/cm^2
4	Drug content	97.91%

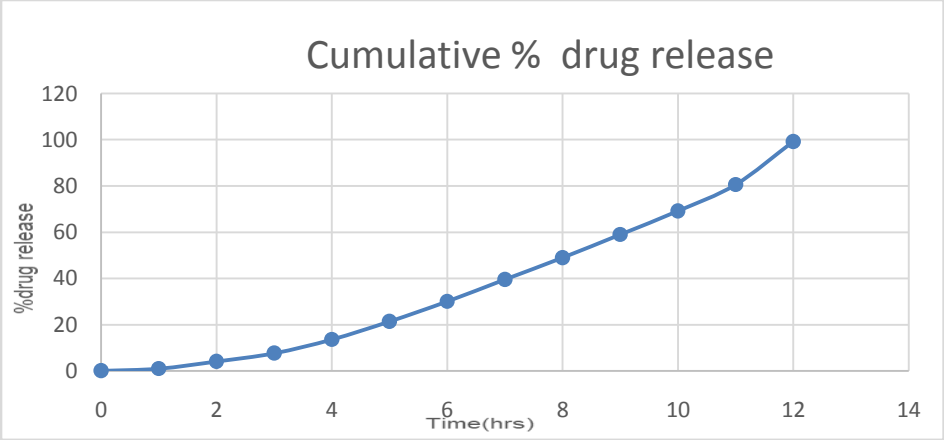

Fig.5 : Dissolution profile of optimized batch F4 (after stability study)

Conclusion

The prepared formulation of a sustained-release matrix tablet containing methocarbamol using various polymer concentrations of Xanthan gum and HPMC K100M prepared matrix tablet exhibits a higher amount of drug content, sustained drug release, and improved stability. The formulated batches were evaluated for the Hardness test, weight variation test, friability test, drug content, and in vitro % drug release. The characterization of the tablet shows satisfactory results of a tablet like weight variation and thickness. The formulation F4 showed the highest amount of drug content. FTIR and DSC studies reveal that there are no interactions between drugs and excipients which means drugs and excipients are compatible with each other. Formulation F4 is optimized batch passes evaluation parameters and maximum % drug release i.e. 100.14 % upto 12 hrs. The percent drug release was found to be within acceptable limits.The rate of percent drug release was seen to be slower in the tablets made with a combination of Xanthan gum and HPMC K100M 10% &15% respectively. F4 formulation was the subject of stability tests, and the results showed that it was stable for 90 days.

Future Scope

The Sustained release dosage forms can increase the bioavailability and half-life of medications while providing effective therapeutic results. Due to these, the frequency of dosing will also reduce and improve patient compliance. Pharmaceutical companies are now utilizing sustained-release dosage forms advantages and growing acceptance by formulating various active pharmaceutical ingredients (APIs) as sustained-release matrix tablets to enhance patient compliance. Considering the future, more drugs are being loaded with sustained-release matrix tablets.

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Conflict of interest

Authorsdeclare no conflict of interest.

References

1. Florence AT, Siepmann J, editors. Modern Pharmaceutics Volume 1: Basic Principles and Systems. CRC Press; 2009 May 28.
2. Modi SA, Gaikwad PD, Bankar VH, Pawar SP. Sustained release drug delivery system: a review. International journal of pharma research and development. 2011 Feb;2(12):147-60.
3. Kaur G, Grewal J, Jyoti K, Jain UK, Chandra R, Madan J. Oral controlled and sustained drug delivery systems. Drug Targeting and Stimuli Sensitive Drug Delivery Systems. Elsevier; 2018. p. 567–626.
4. Brahankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics: A treatise. VallabhPrakashan; 2009.
5. Vijayasree P, Devika GS, Sravani M, Krishna SV, Vali DS. Simple UV Spectrophotometric Estimation of Methocarbamol by Co–Solubilization Technique. Research Journal of Pharmacy and Technology. 2014;7(8):837-9.
6. Sun L, Zhang W, Liu X, Sun J. Preparation and evaluation of sustained-release azithromycin tablets in vitro and in vivo. Asian Journal of Pharmaceutical Sciences. 2014 Jun 1;9(3):155-61.
7. Abd-Elbary A, Haider M, Sayed S. In vitro characterization and release study of Ambroxol hydrochloride matrix tablets prepared by direct compression. Pharmaceutical Development and Technology. 2012 Oct 1;17(5):562-73.
8. Sun L, Zhang W, Liu X, Sun J. Preparation and evaluation of sustained-release azithromycin tablets in vitro and in vivo. Asian Journal of Pharmaceutical Sciences. 2014 Jun 1;9(3):155-61.
9. Pani NR, Nath LK. Development of controlled release tablet by optimizing HPMC: Consideration of theoretical release and RSM. Carbohydrate polymers. 2014 Apr 15;104:238-45.
10. Ofori-Kwakye K, Mfoafo KA, Kipo SL, Kuntworbe N, El Boakye-Gyasi M. Development and evaluation of natural gum-based extended release matrix tablets of two model drugs of different water solubilities by direct compression. Saudi Pharmaceutical Journal. 2016 Jan 1;24(1):82-91.
11. Shah SN, Asghar S, Choudhry MA, Akash MS, Rehman NU, Baksh S. Formulation and evaluation of natural gum-based sustained release matrix tablets of flurbiprofen using response surface methodology. Drug development and industrial pharmacy. 2009 Dec 1;35(12):1470-8.
12. Li L, Sun H, Gao J, Jiang T, Gao Y, Zhang J. Optimization of sustained release matrix tablet of metoprolol succinate using central composite design. Pakistan journal of pharmaceutical sciences. 2013 Sep 1;26(5).
13. Yilma Z, Belete A, Gebre-Mariam T. Formulation and optimization of sustained release floating matrix tablets of salbutamol sulphate using xanthan gum and hydroxypropyl methylcellulose polymer blend. International Journal of Pharmaceutical Sciences and Research. 2015 May 1;6(5):1877.
14. Saurí J, Millán D, Suñé-Negre JM, Pérez-Lozano P, Sarrate R, Fàbregas A, Carrillo C, Miñarro M, Ticó JR, García-Montoya E. The use of the SeDeM diagram expert system for the formulation of Captopril SR matrix tablets by direct compression. International Journal of Pharmaceutics. 2014 Jan 30;461(1-2):38-45.
15. Wadher KJ, Kakde RB, Umekar MJ. Formulation of sustained release metformin hydrochloride matrix tablets: Influence of hydrophilic polymers on the release rate and in vitro evaluation. International Journal of Research in Controlled Release. 2011;1(1):9-16.

16. Kaleemullah M, Jiyauddin K, Thiban E, Rasha S, Al-Dhalli S, Budiasih S, Gamal OE, Fadli A, Eddy Y. Development and evaluation of Ketoprofen sustained release matrix tablet using Hibiscus rosa-sinensis leaves mucilage. Saudi pharmaceutical journal. 2017 Jul 1;25(5):770-9.
17. Kar R, Mohapatra S, Bhanja S, Das D, Barik B. Formulation and in vitro characterization of xanthan gum-based sustained release matrix tables of isosorbide-5-mononitrate. Iranian journal of pharmaceutical research: IJPR. 2010;9(1):13.
18. Hiremath P, Nuguru K, Agrahari V. Material attributes and their impact on wet granulation process performance. InHandbook of pharmaceutical wet granulation 2019 Jan 1 (pp. 263-315). Academic Press.
19. Corti G, Cirri M, Maestrelli F, Mennini N, Mura P. Sustained-release matrix tablets of metformin hydrochloride in combination with triacetyl-β-cyclodextrin. European Journal of Pharmaceutics and Biopharmaceutics. 2008 Feb 1;68(2):303-9.