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Original Article

DESIGN AND EVALUATION OFCARBOXYMETHYL TAMARIND KERNEL POLYSACCHARIDE (CMTKP) CONTROLLED RELEASE SPHEROIDS/PELLETS AND INVESTIGATING THE INFLUENCE OF COMPRESSION

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ABSTRACT

Objective: The aim of the present work was to design Carboxymethyl tamarind kernel polysaccharide (CMTKP) sustain release spheroids of lornoxicam through extrusion/spheronization technique and to evaluate the effect of compression force on same.

Methods: Extrusion/spheronization technique for pellet preparation and tableting for compression of spheroidsinto tablets.

Results: The results of micromeritic properties, hausner's ratio and friability, were within the limit, indicating good flow potential of the prepared spheroids. The drug loaded spheroids were in spherical shape as evidence in SEM photomicrographs. Form the DSC studies it was evident that there was no chemical interaction between the drug used and polymers indicating, that drug was in stable form.The formulation developed using 10% w/w CMTKP, was found to sustain the drug release over a period of 12 h.

Conclusion: From the present work, it can be concluded that the prepared matrix spheroid demonstrates the potential use of MCC and CMTKP blend for the development of controlled drug delivery systems for many water insoluble drugs.

Keywords: Carboxymethyl tamarind kernel polysaccharide (CMTKP) extrusion-spheronization, Roll compacted tablets, Lornoxicam.

INTRODUCTION

The process of extrusion/spheronization is a popular and accepted method of producing spheroids. This process consists of basic five unit operations i.e.,—blending, wet massing, extrusion, spheronization and drying resulting in the formation of spherical spheroids showing a homogeneous surface. Spheroids are agglomerates of bulk drugs and excipients. They consist of small, free-flowing, spherical or semispherical solid units, typically from ~0.5 to 1.5 mm and are intended for oral administration [1, 2, 3]. Thus,multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet[4]. The spheroids offer certain specific advantages over conventional solid dosage forms like- free flow and ease of packing, resulting in reproducible and uniform fill weight of capsules. It has been found that spheroidal particles smaller than 2.4 mm diameter are free from digestive function of the stomach and the closing system of pyloric sphincter of stomach [5,6]. Implants of small cylinders formed by compression from medicated masses are also defined as spheroids in pharmacy [7,8]. Many methods have been reported for the preparation of spheroids: melt spheronization, compaction, globulation drug layering, melt spheronization, globulation, balling, compression, and extrusionspheronization. Among these, extrusion-spheronization is the most popular method [9,10]. Spheroids offer great flexibility in designing and development of pharmaceutical soliddosage form. Spheroids are suitable candidates for coating due to their ideal spherical shape and a low surface area-to-volume ratio [11,12]. Spheroidscontainingdifferent drugs can be blended together and formulated in a single unit dosage form. This approach facilitates the advantage of delivering two or more drugs which are chemically compatible or incompatible, at the same sites or different sites in the gastrointestinal tract [3,13]. The dosage form containing pelletized product can freely disperse in the gastrointestinal tract as a subunit, thus providing the advantage by maximising drug absorption and reducing peak plasma fluctuation. Finally, potential side effects can be minimized without affecting drug bioavailability. It adds another advantage by preventing local irritation derived from high local concentrations of a drug from a single-unit dose, in certain class of drugs. One cheap and naturally derived biopolymer is tamarind kernel polysaccharide (TKP) obtained fromtheTamarindusindica L. seeds. TSP is composed of(1→4)--d-glucan backbone substituted with sidechainsof-d-xylopyranoseand-d-galactopyranosyl(1→2)- d-xylopyranose linked (1→6) to glucose residues. TKP is noncarcinogenic, and biocompatible [14]. It is used as binder, gelling agent, thickening agent, emulsifying agent, and suspending agent in pharmaceutical formulations [15]. In an investigation, Sougata Jana et al. have formulated aceclofenac-loaded chitosan-tamarind kernel polysaccharide interpenetratingpolymeric network microspheres [16]. In present study CMTKP was used as a release modifier in spheroids using Lornoxicamas model drug.

Lornoxicam is a Non-Steroidal Antiinflammatory Drug (NSAID) of the oxicamclass.It has analgesic, anti-inflammatory and antipyretic properties. Lornoxicam is also as a NSAID in relieving symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute sciatica and low back pain. It inhibits prostaglandin biosynthesis by blocking the enzyme cyclooxygenase (both COX-1 and COX-2). Maximum plasma concentrations are achieved after approximately 1 to 2 hours. The absolute bioavailability of Lornoxicam is 90-100%. After administration, Lornoxicamis found in the plasma in unchanged form and as its (it should be 'it is')hydroxylated metabolite. Sustained release formulation is needed for Lornoxicam because of its short biological half-life of 3.0-5.0 h and also to minimize the G.I. disturbances such as peptic ulceration with or without bleeding if present in larger concentration in G.I.tract [17].In the present study modified polysaccharide i.e. CMTKP was used for sustained release of lornoxicam. As natural polysaccharide was available in plenty and due to their low cost, there may be reduction in the cost of dosage form.

MATERIALS AND METHODS

Materials

Carboxymethyl tamarind kernel polysaccharide (CMTKP) was obtained as gift sample from Creative polymer industries, Hindupur, Andhrapradesh, Lornoxicamwas a kind gift from Micro Labs Ltd. (Bangalore, India). Microcrystalline cellulose (MCC), Lactose

anhydrous andAvicel® PH 200 was obtained from LobaChemie (Mumbai, India). All other chemicals and reagents used in the present study were of analytical reagent grade.

Characterization of gum

The viscosity of 1% solution of the CMTKP polysaccharide was determined in distilled water, pH 1.2 and pH 7.2 phosphate buffer using a Brookfield RVDV II+ viscometer (Brookfield Engineering, USA) with spindle # S28, at 50 rpm. The pH of the CMTKP solution (1% w/v in distilled) was determined using digital pH meter (Oakton Benchtop pH 700 Meter). The surface a characteristic of polysaccharide powder wasstudied by scanning electron micrograph (SEM).The powder was sputtered with gold to make the samples electrically connected. The SEM was taken in Joel- LV-5600, USA equipment.

Preparation of drug-loaded spheroids

For the preparation of spheroids, Extruder (EXT-65/037, R.R. Enterprises, Mumbai, India) and Spheronizer (SPH-150/010, R.R. Enterprises, Mumbai, India) were used. In the formulation of spheroids, MCC was used as spheronization enhancer. Here,different batches were prepared like BD-1, BD-2, BD-3, BD-4 BD-5 and BD-6containing MCC-CMTKP-drug in different ratios such as 72.5:2.5:25% w/w, 70:5:25% w/w, 67.5:7.5:25% w/w, 65:10:25% w/w, 62.5:12.5:25% w/w and 60:15:25% w/w.

The powder mixes were prepared as 100 g batches by geometric mixing in polyethylene bag for 10 min.Then the above mixture of dry blend was granulated by using demineralised water as granulation fluid. The wet mass was extruded using cylinder roll type extruder with 1 mmopening diameter at 40 rpm. The obtained extrudates were spheronized in a spheronizer fitted with a cross-hatched rotor plate of 150 mm diameter and 2.5 mm thickness. The resulting spheroids were dried in hot air oven (Memmert 30, Germany) at 40° C for 8 h. For the optimization of spheronization speed, extrudates from all the selected ratios of MCC- CMTKP-drug were subjected to spheronization at different speeds such as 400, 600, 800, 1200, 1400 and 1600 rpm. For optimization of spheronization time, the ideal batch of spheroids was subjected to spheronization at 1600 rpm for different duration of time such as 5, 10 and 15 min.

Characterization of spheroids

Particle size analysis

The particle size of the prepared spheroids was measured using a Malvern mastersizer 2000 version 5.1 (Malvern, UK). The drug loaded Lornoxicamspheroids were dispersed in 1:20 with methanol and measured at temperature of 37°C.

Micromeritic properties

Tap densities of the prepared spheroids were determined using tap density tester and percentage Carr's index was calculated.

Angle of repose

Angle of repose wasassessed by fixed funnel method to know the flowability of spheroids.Lornoxicamspheroids were carefully poured through the funnel until the apex of the conical pile just reaches the tip of the funnel. The radius (r) and height of the pile (h) were then determined. The angle of repose (θ) for samples were calculated using the following Eq. (1):

$$\text{Angle of repose } (\theta) = \tan^{-1}\frac{h}{r} \quad (1)$$

Compressibility

Carr's index is a dimensionless quantity, which proved to be useful to the same degree as the angle of repose values for predicting the flow behaviour. The compressibility of the spheroids was determined by Carr's compressibility index using the Eq. (2) given below [18].

$$\text{Carr}'\text{s index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \quad (2)$$

Scanning Electron Microscopic (SEM) studies

SEM photographs were taken with a scanning electron microscope Model Joel- LV-5600, USA, at the required magnification at room temperature. The photographs were observed for morphological characteristics and to confirm spherical nature of the spheroids.

Spheroid size

Spheroid size was determined using an image analysis system. Photomicrographs were taken with a digital camera (Sony, Cyber-shot, DSC-HX20V/B, Japan).The obtained images were processed by image analysis software (AnalySIS®; Soft Imaging System, Münster, Germany)to characterize each individual spheroid by mean Feret diameter (FD) (average of 180 calliper measurements with an angle of rotation of 1°), aspect ratio (AR) (ratio of longest Feret diameter and its longest perpendicular diameter) and two-dimensional shape factor (e_R) as in Eq. (3):

$$e_R = \frac{2\pi r}{P_m} - \sqrt{1 - \left(\frac{b}{l}\right)^2} \quad (3)$$

wherer is the radius, $P_m$the perimeter, l the length (longest Feret diameter) and b the width (longest perpendicular diameter to the longest Feret diameter) of the spheroid [19].

Differential Scanning Calorimetry (DSC)

DSC is a technique in which the difference in heat flow between the sample and a reference is recorded against temperature. All dynamic DSC studies were carried out on Mettler-Toledo(DSC 822e). A few milligrams of sample, were hermetically sealed into aluminium pans and heated under nitrogen atmosphere with the heating rate of 10° C/min [20].

Evaluation of spheroids

Friability

Friability was determined by using the Roche friabilatortester (Electrolab, Mumbai, India). 10 g of spheroids were subjected to impact testing at 25 rpm for 4 min. The abraded samples were sieved and the spheroids retained on the sieve were weighed and percent friability was calculated from the difference in the weight of the spheroids before and after friability [21].

Percentage yield

The yield of spheroids was determined by the whole weight of spheroids formed against the combined weights of drug and polymer. The formula for calculation of % yield is as follows Eq. (4):

$$\%\ \text{yield} = \left(\frac{\text{wt.of pellets}}{\text{wt.drug+wt.of polymer}}\right) \times 100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

Drug loading and entrapment efficiency

Drug loading is important with regard to release characteristics. Generally, increased drug loading leads to an acceleration of the drug release. Drug entrapment efficiency represents the proportion of the initial amount of drug, which has been incorporated into the spheroids. To assess the entrapment efficiency, specific amount of crushed spheroids were suspended in 100 ml of pH 7.2 phosphate buffer with constant agitation at room temperature for 24 h. Finally, the solution was filtered through Whatman filter paper, drug content was determined spectrophotometrically, at the wavelength of 379 nm using 7.2 pH phosphate buffer as blank. The entrapment efficiencywas calculated by using the Eq. (5):

$$\%\ \text{Drug entrapment} = \left(\frac{\text{Calculated drug content}}{\text{Theortical drug content}}\right) \times 100 \quad (5)$$

Percent drug loading was calculated by using the following Eq. (6):

$$\%\ \text{Drug Loading} = \left(\frac{\text{Amount of drug in sample pellets}}{\text{wt.of pellets}}\right) \times 100 \quad (6)$$

Sieve analysis

Particle size distribution was determined by sieve analysis. 75 g of sample was sieved using a vibratory sieve shaker (Electrolab, Mumbai, India) at an amplitude 10 for 10min. 1400, 1000 and 710 μm

sieves were used and the fraction retaining on each screen was weighed and expressed as a percentage of the total weight.

Compression of spheroids

The optimized batch Lornoxicamspheroids were mixed with 20% filler (Avicel® PH 200) and 10% w/w lactose anhydrous and slugs were prepared, then the prepared slugs were passed through Multimill screen (0.5") (Cip Machineries Pvt. Ltd., Ahmedabad, India). The granules were sieved through #40 sieves. The final granules were blended with 1% magnesium stearate and compressed for 1 min with different predetermined loads (5, 7 and 10 Ton's) using a hydraulic hand press (KBr press, TsiTchno, Mumbai, India) with 12.7 mm die and flat-faced punches. The hardness of the tablets was determined using a Monsanto hardness tester (Cadmach, Ahmedabad, India). The percentage of friability of the tablets was determined using Roche tablet friabilator (Indian Equipment Corporation, Mumbai, India) operated for 100 revolutions. The weight variation test for the tablets was performed by the official method as directed in USP [22].

***In Vitro* dissolution**

To study the in vitro dissolution profile, spheroids equivalent to 100 mg of Lornoxicamwere filled in hard gelatin capsules. Dissolution studies were carried out using dissolution apparatus USP-XXIII attached with paddle (Electrolab, Mumbai, India). Freshly prepared phosphate buffer of pH 7.2 (900 ml) was used as dissolution medium at 37±1°C. The paddle was rotated at 50 rpm. The 5 ml of samples were withdrawn on definite time intervals and immediately replaced with an equal quantity of fresh buffer. The amount of drug released was quantified using the high-performance liquid chromatography (HPLC) method. The samples containing drugs were injected directly to the HPLC system. The HPLC system comprises of SHIMADZU LC-2010 AHT with auto sampler and UV-Visible detector. Chromatographic separation was achieved using a Phenomenex C 18 column (250 x 4.6 mm i.d., 5 µm particle sizes). The Lornoxicamin samples was analysed at 379nm.

Stability studies

The ideal batches of the formulated spheroids containing 100 mg Lornoxicamin capsules were blister packed and then kept in the stability chamber at 25°C/60% RH, 40°C/75% RH and room temperature. Samples were withdrawn at 15, 30 and 60 days and evaluated for their physical appearance, friability and drug content [23].

RESULTS AND DISCUSSION

Here spheroid cores were obtained by means of extrusion and spheronization. From solubility studies it has been found that CMTKP is insoluble in water and phosphate buffer (pH 7.2) this may be attributed to the hydrophobic nature. Because of its hydrophobic nature it has shown no swelling in water and phosphate buffer (pH 7.2). The polysaccharide was characterized for viscosity, pH and surface characterization by SEM. The viscosity of 1% w/v solution was found to be 38 cP in distilled water and 40 cP and 45cP in pH 1.2 and 7.2 phosphate buffer. This, higher viscosity enables the sustained release of drug from formulations. The pH of CMTKP solution was found to be 4.5±0.29, which is advantageous for formulation of pharmaceutical dosage forms as it would not cause irritation to the mucous membrane and epithelium of the gastrointestinal tract[24]. The SEM photograph of polysaccharide Fig. 1 depicted the crystalline nature and smooth surface with narrow range of particle size distribution. This narrow particle size distribution boosts the formation of compacted packing by filling the void with fine particles.

Table 1 and Table 2 shows the process of optimization of extrusion and spheronization. In concentration of 2.5 to 15% w/w of CMTKPspheroids were formed with narrow range of size distribution. As the concentration of polymer increases, the increase in the mean size range of spheroids was observed with decreased yield in the desirable size range [25].At CMTKP level above 15% w/w, the cohesiveness of the extrusion mass increased, which resulted in increased resistance toflow through the extruder die even at appropriately wetted levels.

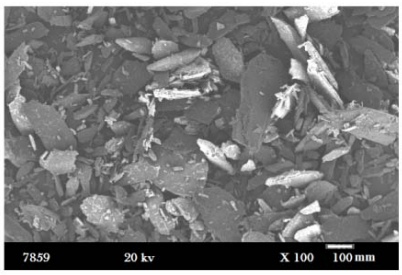

Fig. 1: SEM of CMTKP powder (100X)

On increasing the water levels, the easy extrusion of wetted mass through the die was witnessed, but the resulting extrudates were too tacky for further processing. Extrudate suitable for further processing was obtained only when CMTKP levels in the formulation were below 15% w/w. However, at CMTKP level above 15% w/w the resistance of the extrudate pieces to round up in the spheronizer was increased. Based on these preliminary studies, the CMTKP levels were chosen to be below 15% w/w in the formulations [26].

Table 1: Optimization of Lornoxicampelletsspheronization speed

Mcc-Cmtkp-drug ratio	Spheronization speed (rpm)	Spheroid description
72.5:2.5:25	400	Dumbbell shape
	600	Dumbbell shape
	800	Dumbbell shape
	1200	Dumbbell shape
	1400	Spheroids with narrow size range
	1600	Spheroids with narrow size range
70:5:25	400	Dumbbell shape
	600	Dumbbell shape
	800	Dumbbell shape
	1200	Dumbbell shape
	1400	Spheroids with narrow size range
	1600	Spheroids with narrow size range
67.5:7.5:25	400	Dumbbell shape
	600	Dumbbell shape
	800	Dumbbell shape
	1200	Dumbbell shape
	1400	Spheroids with narrow size range
	1600	Spheroids with narrow size range
65:10:25	400	Dumbbell shape
	600	Dumbbell shape
	800	Dumbbell shape
	1200	Dumbbell shape
	1400	Dumbbell shape
	1600	Spheroids with narrow size range
62.5:12.5:25	400	Dumbbell shape
	600	Dumbbell shape
	800	Dumbbell shape
	1200	Dumbbell shape
	1400	Dumbbell shape
	1600	Spheroids with narrow size range
60:15:25	400	Dumbbell shape
	600	Dumbbell shape
	800	Dumbbell shape
	1200	Dumbbell shape
	1400	Dumbbell shape
	1600	Spheroids with narrow size range

Table 2: Optimization of Lornoxicampelletss pheronization time

MCC-drug-polymer ratio	Spheronization speed (rpm)	Spheronization time (min)	Spheroid description
72.5:2.5:25	1400	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
70:5:25	1400	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
67.5:7.5:25	1400	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
65:10:25	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
62.5:12.5:25	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
60:15:25	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids not formed
		20	Spheroids formed

In the present study, spheronization appeared to have occurred by the mechanism described by Rowe [27]. It was observed that extrudate broke into small cyclindrical particles, because of the friction of spheronization plate, further which went through several shape changes process, i.e., cylinders with rounded ends, dumb-bells, ellipsoids and finally spheroidal [28].

Another key factor affecting the extrusion process is the wet massing liquid content. The right amount of water levels need to be optimized for extrusion mass. It was observed that if the moisture content of the extrusion mass was less than the lower limit, the mixtures do not flow through the extruder barrel. Further, during the spheronization, a lot of dust was generated resulting in a large yield of fines. It may be explained due to lack of pastic properties in the wet mass, because of lower water content. Conversely, increasing the water levels, facilitates easy extrusion of mass by reducing viscosity, as wetter mass becomes softer and less force is required for extrusion. However, above the upper limit of moisture content, the mass gets extruded satisfactorily, but it resulted in large agglomerates on spheronization[28]. It has been found that, the surface of spheroids gets smoother with increasing the amount of wet massing liquid [29].

The influence of the spheronization speed, time and spheroid properties has been extensively reviwed by several authors. The main variables affecting spheroids characteristics are- formulation load, residence time, peripheral velocity and geometry of spheronization plate. For formation of suitably shaped spheroids, require the extrudates with sufficient plastic properties, that are spheronized by the forces that occurred from the movement of the friction plate of spheronizer. When the polymer concentration was increased, the longer rod shaped spheroids were obtained at low speed and spheroids with decreased sphericity with larger size were obtained at higher speed[30,31,32].In the process of spheronization speed optimization, it was found that at lower speed, more number of rod and dumbbell shaped particles were obtained due to the rheological properties of CMTKP, where the extrudates resist to convert into spheroids. Further increasing the spheronization speed to 1600 rpm, the more energy is imparted to the particles which results in more force during collision.

The, speed depends on the characteristics of the product being used and particle size required. In general, smaller particles require higher speed while bigger particles (with higher mass which result in more force during a collision) require low speed. However, when the spheronization speed was increased, the yield was reduced due to high centrifugal forces on the extrudes which resulted in excessive breaking and converting into powder form[33].

Following the optimization of speed the spheronization time was optimized. It was found that at shorter spheronization time (i.e., less than 10 min); extrudes were not converted into spheroids completely with lower yield. From the experimentationas shown in Table 2, it was found that at spheronization time of 15 min at 1600 rpm, was sufficent to produce spheroids with maximum yield and acceptable sphericity. Using longer spheronization time did not improve the spheroid sphericity and yield, but promoted broadening of spheroid size distribution and leading to spheroid agglomeration due to combining with fine particles that produced in the process [33].

The micromeritic properties of different batchesas shown in Table 3, like average size, angle of repose, tapped density, granule density, carr's index and friability revealed no significant difference among the different batches. Thus, from the above micromeritic data it is evident that blends of different formulation batches prepared with MCC and CMTKP possess comparable flow properties and carr's index. In size distribution analysis, it was found that spheroids were with in size range of 769 – 1368 µm with normal size distribution with average particle size of spheroids1239 µm. From the SEM of spheroidsas shown in Fig. 2, it clearly depicts that spheroids exhibited spherical shape with smooth and non-porus surface.

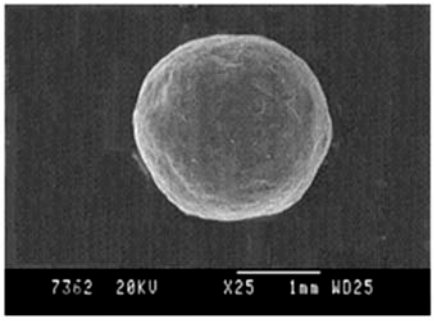

Fig. 2: SEM of the formulated spheroid (magnification 25X)

The bulk densities of spheroids were found to be in between 1.04 – 1.07 g/cc, which indicates close packing arrangement because of narrow particle size distribution. The friability values for all batches were found to be within the limits. This may be due to smooth surface and spherical shape as evidenced in SEM of spheroid. Angle of repose for all batches were ranged between 23.45^0 - 26.30^0 indicating good flow properties of spheroids which can be attributed to spherical shape and smooth surface of spheroids.

DSC studies were carried out for lornoxicam and its combination with polymers in 1:1 ratio and the thermograms obtained are presented in Fig. 3. From the thermograms it was evident that decomposition temperature of lornoxicam (218.74 °C) was not changed when a mixed with excipients (219.79 °C)showen in Fig. 3. Hence, it may be inferred that there is no interaction between lornoxicam and polymers used in the preparation of pellets.

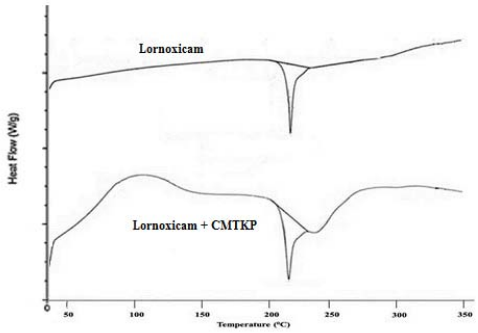

Fig. 3: DSC thermogramof lornoxicam and lornoxicam and polymer

Drug loading and encapsulation efficiency of the spheroids are given in Table 4. Drug loading among all formulations were in the range of 19.59±1.12 - 22.39±0.39%. Drug loading was found to be the least in formulation BD-4and highest in formulation BD-1. The entrapment efficiency of formulation BD-3 (96.09±0.21%) was found to be highest among all formulations. The extent of drug loading appears to influence the particle size distribution of spheroids. When the drug loading is high, the proportion of larger size particles formed are also high.The weight distribution of the different pellet formulation is presented in Fig. 4, indicating the pellet yield (710-1400 µm fraction), in different size range.

Concentrations of CMTKP

The spheroids were filled in hard gelatin capsules and evaluated for in-vitro drug release study. The drug dissolution profiles of matrix spheroids formulated using CMTKP are shown inFig. 5. It could be seen that increasing the polymer concentration level from 2.5 to 15% caused significant reduction in the drug release. A controlled release of drug from the CMTKPspheroids was observed and can be attributed to the hydrophobic barrier limiting access of water and dissolution of drug. Kiortsis and co-workers[34]reported that, the drug release from the dosage form comprising of cellulosic and hydrophobic matrix, follows three steps. The first step is the penetration of the dissolution medium into the dosage form (hydration). The second step is erosion of the matrix and the third step is the transport of the dissolved either through the hydrated matrix or from the parts of eroded area of dosage form, to the surrounding dissolution medium.

Table 3: Characteristics of spheroids

Formulation code	Averagesize(µm)	Angle of repose θ⁰	Tapped density (g/cm³)	Granule density (g/cm³)	Carr's index(%)	Friability(%)
BD-1	1125±0.56	26.54±0.92	0.84±0.64	1.06±0.88	9.12±0.32	0.53±0.78
BD-2	1179±0.45	25.42±0.25	0.86±0.92	1.07±1.78	8.79±0.99	0.52±0.45
BD-3	1345±0.23	23.45±0.88	0.90±1.43	1.05±1.45	9.39±0.53	0.43±0.82
BD-4	1239±0.55	26.30±0.65	0.89±1.01	1.05±0.96	8.93±0.98	0.47±0.36
BD-5	1238±1.02	25.25±0.46	0.83±0.55	1.04±0.72	8.76±1.76	0.45±0.78
BD-6	1279±0.92	25.98±0.74	0.83±0.82	1.07±0.81	8.69±2.01	0.49±0.22

Table 4: Drug Loading and entrapment efficiency of different formulations

Formulation	Drug Loading (%)	Entrapment Efficiency (%)
BD-1	22.39±0.39	91.42±1.12
BD-2	20.53±0.57	92.94±0.71
BD-3	21.09±1.44	96.09±0.21
BD-4	19.59±1.12	94.26±1.09
BD-5	19.92±0.51	95.12±1.63
BD-6	18.81±0.87	95.94±1.90

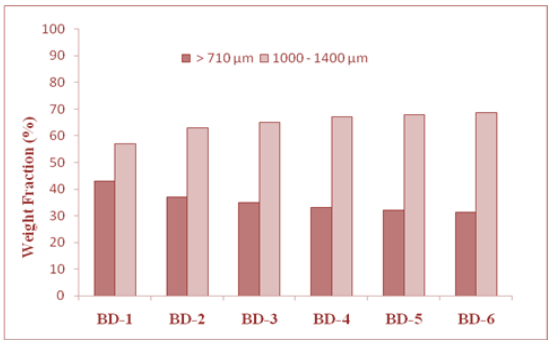

Fig. 4: Weight distribution (%) graph of spheroid formulations containing different

Concentration of CMTKP (2.5%, 5%, 7.5%. 10%, 12.5% and 15% w/w)

From the in vitro release data, it was found that formulations BD-1, BD-2 and BD-3 containing CMTKP in concentration 2.5% w/w, 5% w/w and 7.5% w/w released 97.20±1.5%, 79.35±1.7% and 66.89±1.4% of drug at the end of 7 h study, indicating that the polymer in each formulation was insufficient to sustain the drug release. The release of drug from the BD-4 batch prepared with 10% w/w CMTKP concentration was extremely significant in comparison to other batches. The amount of drug released at the end of 12 h was found to be 98.13±0.9%.This might be due to higher concentration of the CMTKP, which may be attributed to slower penetration of dissolution medium in the matrices.

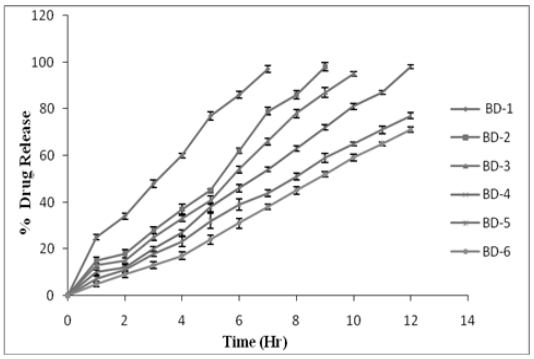

Fig. 5: In vitro dissolution profile of Lornoxicamspheroids prepared with different

The formulations BD-5 and BD-6 consisting 12.5% w/w and 15% w/w CMTKP shown insufficient release at the end of 12 h because of high polymer concentrations.From Fig. 5. it can be observed that for all the formulations, drug release is inversely proportional the to concentarion of rate retarding matrix former (polymer) present in the matrix system i.e., the rate and extent of drug release decreases with increase in total concentration of polymer.Here all the parameters were run for 6 times (n=6). The difference in mean of % drug release between batch series was significant ($p < 0.05$). From the above observation the drug release retardation from the

formulations were in the order BD-1<BD-2< BD-3<BD-4 <BD-5<BD-6.A formulation prepared with 10% w/w CMTKP i.e., BD-4 was identified as an ideal batch based on its physicochemical and release characteristics. The drug release data of optimized formulationi.e.,BD-4 was subjected to release kinetic models, which indicated that batch BD-4 followed zero-order (R^2=0.993) release kinetic model.

The release of Lornoxicamfrom roller compacted tablets showed compression force dependent release. Damage of the spheroids as its conversion into powder form, is the main reason for compression force dependent release. Tablets prepared at different compression force played a key role in dissolution of drug.

It was found that as compression force increases the porosity decreases and resulted tablets were harder with lower dissolution rates as shown in Fig.6. The mechanism of drug release from water insoluble matrix i.e., MCC is believed to be diffusion controlled process as defined by fick's law, which is dependent on porosity factor and tortuosity factor.

These factors can be changed by altering the compression force. It was shown during the dissolution studies. The different characteristics of compressed tablets are given in Table 5. The hardness was found to increase with increase in compression force it was in order 5 Ton < 10 Ton < 12.5 Ton. The friability and weight variation tests were also within pharmacopoeial limits.

Table 5: Characteristics values of compressed tablets

Parameters	Compression force's		
	5 Ton	10 Ton	12.5 Ton
Weight Variation (mg)	523±0.155	526±0.127	523±0.089
Hardness (Kg/cm^2)	4.4±0.114	6.9±0.259	8.4±0.263
Friability (%)	0.8±0.079	0.6±0.121	0.4 ±0.147

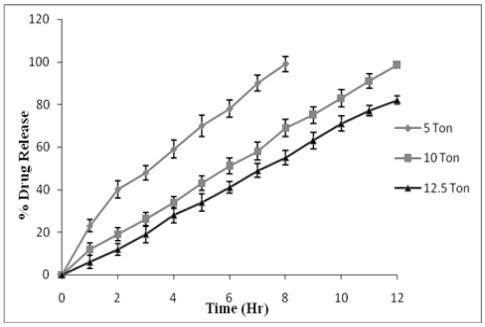

Fig. 6: In vitro dissolution profile of Lornoxicamtablets prepared with different predetermined compression loads (5, 7 and 10 Ton's)

Table 6: Stability evaluation of Lornoxicampelletsstored at different temperatures and relative humidity conditions (mean ±S.D. n = 3).

		25°C/60% RH			40°C/75% RH		
	Day	Day's			Day's		
	0	15	30	60	15	30	60
Physical Appearance	White color	No significant change	No significant change	No significant change	No significant change	No significant change	No significant change
Friability (%)	0.47±0.36	0.45±0.16	0.51±0.26	0.54±0.32	0.48±0.22	0.54±0.14	0.56±0.19
Drug Content (%)	97.41±0.52	97.11±0.12	97.31±0.19	97.33±0.55	97.09±0.24	98.21±0.27	97.41±0.26

Stability studies of formulated Lornoxicamspheroids with 10% w/w CMTKP were carried out at 25°C/60% RH and 40°C/75% RH. The spheroidal formulation was subjected to various evaluation parameters and the results obtained were within the range. The results are given in Table 6.

There was no significant change in physicochemical properties of the spheroids. The loss in total weight in friability test was in the range of 0.45±0.16 – 0.56±0.14%. The percent drug content for different formulation varied from 97.09±0.24 – 98.21±0.27%. Based on the results it can be concluded that the formulated Lornoxicamspheroids were stable over a period of 60 days.

CONCLUSION

This study illustrated the potential of novel CMTKP as spheronization aid in the formulation of sustained release spheroids by extrusion/spheronization. The method which was employed is simple, rapid and economical.The results of micromeriticproperties, hausner's ratio and friability, were within the limit, indicating good flow potential of the prepared spheroids.The drug loaded spheroids were in spherical shape as evidence in SEM photomicrographs. Form the DSC studies it was evident that there was no chemical interaction between the drug used and polymers indicating, that drug was in stable form.

The formulation developed using 10% w/w CMTKP,was found to sustain the drug release over a period of 12 h. The conclusion of the study is that the, rate of drug release can be modulated by varying the concentration of polymer included in the formulation. In case of roll compacted tablets the compression force dependent drug release was observed.From the present work, it can be concluded that the prepared matrix spheroiddemonstrates the potential use of MCC and CMTKP blend for the development of controlled drug delivery systems for many water insoluble drugs.

CONFLICT OF INTERESTS

Declared None

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