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FORMULATION AND EVALUATION OF EXTENDED RELEASE TABLETS OF TOLMETIN

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ABSTRACT

The main objective of the present research work is to formulate the Tolmetin Extended Release Tablets. Tolmetin is a non-steroidal anti-inflammatory drug (NSAID) that is effective in treating fever, pain, and inflammation in the body. Tolmetin blocks the enzyme that makes prostaglandins (Cyclo-oxygenase), resulting in lower concentrations of prostaglandins. As a consequence, inflammation, pain and fever are reduced. At present the tablets are available in the market uses as multi unit particulate systems to deliver the drug at a controlled rate over 24 hours. The present research endeavor was directed towards the development of Extended Release Tablets to be taken twice daily. The formulation of Tolmetin extended release Tablet is important to give prolonged activity in the prolonged drug release in an Extended Period of Time for the Long Term Therapeutic activity. The Formulation of the extended Released Tablets were prepared by using Suitable Excipients such as Hydroxypropyl methylcellulose; HPMC E3, HPMCK15M, HPMC K100M, hydroxy Ethyl Cellulose, povidone, colloidal silicone dioxide, Magnesium Stearate. This Tolmetin extended release tablets were prepared by using Wet Granulation Method. The Prepared extended release Tablet is Evaluated In terms of bulk density, tapped density, angle of repose, Carr's Index and, hardness test, weight variation test, variability test and in vitro study. The hardness, weight variation, and friability these values are within the pharmacopeia limit. The finalized formulation was subjected for in vitro dissolution and compared with the innovator (Tolectin^{R}600) to produce an equivalent product and stability studies performed at 40^0C / 75% for 2 months. Stability samples were evaluated initially and after 2 months. The results were compared with the pre-determined specifications. All the results were found to be satisfactory.

KEYWORDS

Extended release tablets, Tolmetin and NSAID˙s.

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INTRODUCTION

Oral drug delivery

Oral drug delivery is the most popularly utilized routes of administration among all the routes that have been explored for the Systemic delivery of drugs via various pharmaceutical products of different dosage forms[1].

The treatment of illness has been accomplished by administering drugs to the human body via various pharmaceutical dosage forms, like tablets. These

traditional pharmaceutical products are still commonly seen today in the prescription and over-the-counter drug marketplace. To achieve and maintain the drug concentration in the body within the therapeutic range required for a medication, it is often necessary to take this type of drug delivery system several times a day. This results in a significant fluctuation in drug levels.
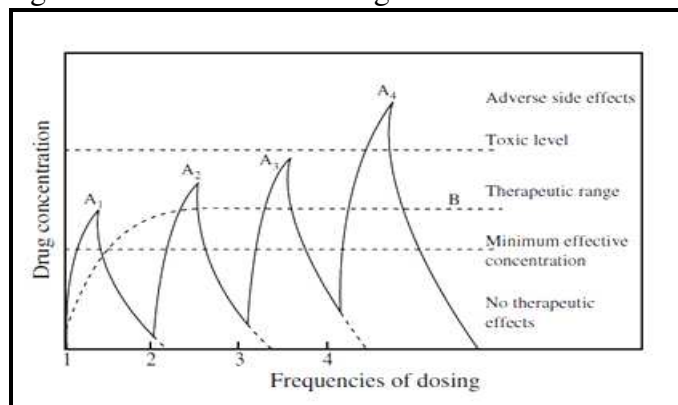

Figure No.1: Drug concentration profiles in the systemic circulation as a result of taking a series of multiple doses of a conventional drug-delivery system (A1, A2, . . .) In comparison with the ideal drug concentration profile (B)[2].

[3-4]Controlled Drug Delivery Systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity and improved patient convenience[5,6]. The main objective of controlled drug delivery systems is to develop the effectiveness of drug therapies[7]. Delayed and extended release (DR) systems release a bolus of the drug after a predetermined time in a predetermined location, i.e. it will takes some time for drug release after administration. E.g. Enteric coated tablets and pulsatile release capsule[8].

MATERIALS AND METHODS[9-28]
Methodology
Direct compression
Direct compression is a popular choice because it provides the shortest, most effective and least complex way to produce the tablets. The manufacturer can blend an API with the excipient and the lubricant, followed by compression, which

makes the product easy to process. No additional processing steps are required. Moisture or thermo labile ingredients, which would be contraindicated in wet granulation, can also be used in this type of process. However, it does require a very proper selection of excipients in comparison to granulation processes because the raw materials must have good flowability and compressibility for getting desirable tablets. If the formulation contains a large amount of the API which affects the quality of tablets. At the same time, it contains low amounts of API need to be incorporated in to tablets by adding large amount of excipients to get desirable properties. For instance, segregation of the different components may occur. That results unequal distribution of the tablet ingredients being fed to the press, and it causes batch to batch variations of the manufactured tablet. One of the major risk factors for segregation is the particle size variation in direct compression formulations, in which active ingredients tend to be at the fine form. Other bulk powder properties are also important for successful tabletting, such as good flowability, and all of these factors combine to place a high requirement on the excipients used for direct compression.
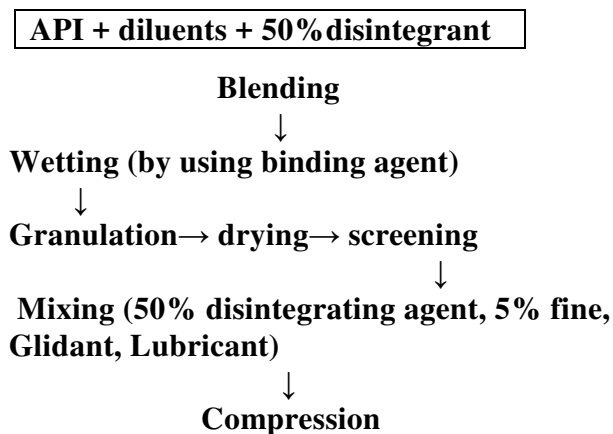
Granulation
If a powder blend's properties are not suitable for direct compression tabletting, manufacturers will select granulation processes to get the desired flowability and low dustability. These properties are required to minimize tablet weight variations, granulation process is nothing but powder blends are converted in to large aggregates and ensure increases the density for high tablet filling weight and high moldability for hard tablet manufacture.

Granulation increases the particle size of the tablet formulation's bulk powder, decreases the segregation problems. This results in increases the flow property of the formulation. However, granulation is a more time-taking process compared with direct compression and there is also a risk of product cross-contamination and product loss during the different processing steps (granulation, drying, sieving). All of these factors can increase costs compared with direct compression, but we can

get stable and robust products by using granulation process when compared with direct compression.

Dry granulation is more flexible than direct compression. Compared with wet granulation, however, it has a shorter, more cost-effective manufacturing process. Because it does not entail heat or moisture, dry granulation is especially suitable for active ingredients that are sensitive to solvents, or labile to moisture and elevated temperatures.

Wet granulation process:

The stages involved in the wet granulation process

API + diluents + 50%disintegrant

Blending

↓

Wetting (by using binding agent)

↓

Granulation→ drying→ screening

↓

Mixing (50% disintegrating agent, 5% fine, Glidant, Lubricant)

↓

Compression

Evaluation of Tolmetin core tablets
Pre-compression studies
Which includes,
Particle size distribution of the granules
Particle size distribution of granules is determined by sieve analysis employing stack of sieves after granules had been weighed 34g and the granules were shaken for 10 minutes. The quantities of granules on each sieve were obtained gravimetrically.

Evaluation of bulk and tapped density of the granules
The known quantity of granules are transferred in to a measuring cylinder, the volume before tapping is represents the bulk density while the volume after tapping represents tapped density, hausner's ratio, carr's index used to determine the flow properties of granules were obtained from the equation.

Hauser's ratio=Tapped density / bulk density
Car's compressibility index= tapped density – bulk density /tapped density × 100

Assessment of rate of flow and angle of repose
A sample method where by weighed quantity of granules from each batch was allowed to flow through an orifice (funnel) at a fixed height was used to determine the flow rate. The time taken for the weighed granules to flow of completely from the orifice was recorded. This was performed in triplicate. Flow rate was obtained by equation below.

Flow rate = wt of granules /time (sec)
Angle of repose (tan θ) = h/ r

Compression of granules
The granules were blended with the disintegrate (micro crystalline cellulose), glidants (colloidal silicon dioxide), lubricant (Mg stearate). The blend was compressed using a single punch tableting machine with a punch diameter 0 .75 cm set at 933 Pa (N/m²). The dry volume was to correspond to the weight of the tablet to ensure that 600mg Tolmetin is obtained.

Post compression parameters
This includes.

Uniformity of weight and diameter of tablets
20 tablets were randomly selected from each batch and assayed gravimetrically as an individual tablet basis. The mean weight as well as standard deviation were calculated. The diameter of tablets were determined by using Vernier calipers.

%deviation= individual weight-average weight X 100
　　　　　　　　　Average weight

Mechanical strength of tablets (hardness)
Although, the crushing strength test is non compendid .it is undertaken to determine the ability of the tablets to withstand pressure during handling, packaging and transportation. A Monsanto tablet hardness test was employed to determine the mechanical strength of the tablets. The average force required to crush the tablet from each batch was obtained.

Friability testing if tablets
To evaluate the degree of friability of the tablets from each batch, ten tablets were randomly

selected, dusted and weighed. The tablets were placed in a Roche friabilator and subjected to its tumbling action at 25 revolutions per minute for 4 minutes. Then after, the tablet were once again dusted and reweighed to determine the % loss of weight.

$$\text{Friability} = \frac{\text{weight of the tablet before test- weight of the tablet after test}}{\text{Weight of the tablet before test}} \times 100$$

Disintegration studies of tablets

Six tablets from each batch were utilized for disintegration studies in distilled water at 37°C using an educational sciences – disintegration apparatus. The disintegration time was taken to be the time where no granule of any tablet was left on the mesh of the apparatus.

In-vitro drug release studies

In-vitro drug release studies were undertaken using USP apparatus 2 (paddle method). The dissolution medium was 900 ml phosphate buffer of pH 6.8 at 37°c for 6 hr. In all experiments, 5 ml of sample was withdrawn at 30 min interval and replaced with fresh medium to maintain sink condition .samples were filterd and assayed spectrophotometrically at 332 nm.

Data analysis

Simple statistical analysis was utilized for content uniformity of weight, uniformity of diameter and uniformity of thickness while dissolution efficiency (DE) was used for the vitro dissolution studies.

Drug content

The tablets were powdered and 600 mg equivalent wt of Tolmetin in tablet powder was accurately weighed and transferred into 100 ml volumetric flask. Initially, 10ml of phosphate buffer of pH 6.8 was added and shaken for 10 min. thereafter; the volume was made up to 100 ml with buffer. Subsequently, the solution in volumetric flask was filtered, and 1 ml of the filtrate was diluted and analyzed ay 332 nm using UV-visible spectrophotometer. The drug content of the each sample was estimated from their previously prepared standard curve.

RESULTS AND DISCUSSION

By the above results it was observed that the 81.5% of particles are retained on the #140 mesh which have 106 µm aperture size and 83.60% of particles are passed through the #100 mesh which have 150 µm aperture size. Therefore it was concluded that major amount of particles have its size range of 150 µm to 106 µm.

Standard Calibration Curves

The λ_{max} was obtained at 271nm in methanol, at 332nm in phosphate buffer (pH 6.8). The standard calibration curve for Tolmetin with regression value of 0.999. The relation between drug concentration and absorbance is linear and the curve obeys Beer - Lambert's law within the concentration range of 5 to 40μg/mL of Tolmetin. The calculation of in-vitro drug release and assay was based on this calibration curve.

From the above Drug–Excipient compatibility studies data, it is clear that Tolmetin is compatible with all the excipients tested above.

Since there was no interaction (or) physical change observed between the drug and all other excipients, the selected excipients were found to be compatible with the drug. Based on the above results and innovator product (Tolectin^R 600), the selected excipients were used in the following categories for the development of formulations.

Evaluation of Tolmetin Blend

Tolmetin Blends were formulated by using direct compression method in F1 and wet granulation method for F2-F8.After the preparation of the Tolmetin blends in each formulation, all the preformulation studies were performed and the results were tabulated in the Table No.7.

Flow properties were determined by calculating various parameters like bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose. From the results obtained above and comparing the values with their respective limits, the following conclusions have been made.

1. Trial batch F1 has been formulated by using direct compression method, the blend showed poor flow property because API concentration was higher than excipients used in the formulation development. Therefore, blend was not passed from the hopper, hence it was concluded that direct

compression method was not suitable for further development.

2. Trials from F2 to F8 has been formulated by using wet granulation method by increasing the amounts of binder, disintegrants, lubricants have been added to increase the flow property.

3. The values of angle of repose within the range of 25- 30, were indicating good flow properties of the blend. The bulk density values ranged between 0.627±0.015 to 0.785±0.008 g/cm3 and the tapped density values ranged between 0.679±0.006 to 0.862±0.231 g/cm3. The result of Carr's Index range from 7.608±0.075% to 10.28±0.009%, suggests excellent flow characteristics of the blend. Hausner's Ratio range from 1.001±0.009% to 1.381±0.165% which indicates the good flow property of Blend. It was showed that there was no sticking of materials to the walls of the hopper and were free flowing. Hence it was concluded that the wet granulation was suitable for compression.

Evaluation of Tolmetin Uncoated Tablets

The tablets of different formulations of Tolmetin were subjected to evaluation tests such as tablet weight, thickness, and hardness and disintegration time. All the results were shown in the tables. 8 respectively.

F2 and F3 showed poor tableting parameters i.e., their Friability values >1 because of low binding quantity. From the above results, all the parameters of tablets from various trial batch formulations from F4 to F6were found to be within the limits of US Pharmacopeia.

a) Average weight of the tablet was within the range of 620-633 + 5 mg.

b) Thickness was within the range of 6 – 6.4 mm.

c) Hardness was within the range of 8 – 11 Kg/cm2

d) Friability was below 1% as per IP specifications.

e) Disintegration time ranges from 8 min to 14 min.

Dissolution Profile of Uncoated Tablets of the Trial Batches in Ph 6.8 Buffer. In F1 which was formulated using direct compression, Sticking and picking problem has been observed during compression process. Hence it was decided to carry out the further process by wet granulation method.

Formulation F2 was formulated by wet granulation. Sticking and picking was not observed with wet granulation and also its free of all physical problems, hence wet granulation method was selected for the formulation of extended release tablets.

Hydroxypropymethylcellulose, Hydroxyethyl Cellulose were used as controlled release polymers in the formulation of extended release tablets of drug by wet granulation. Polymer concentration was optimized initially by keeping rest of all ingredients constant. Only diluents were varied to adjust the tablet weight.

Tablets were prepared by using different polymers namely Hydroxypropy methylcellulose (HPMCK15M CR, HPMC K100M CR), Hydroxyethyl Cellulose (HEC) and their combination in the formulations of F3 to F5 respectively. On using the high viscosity polymer grades of HPMC (HPMC K100M CR) and HEC it was observed that the initial burst release was slightly controlled (F3, F4). But the drug release could not be extended to 12 hours as about 90% of the drug got released at the end of 6 hours.

In next trail formulations (F5 and F6) HPMC K15M CR was used as a rate retarding polymer. Tablets were fabricated using two different concentrations of HPMC K15M CR 80mg, 100mg per tablet respectively.

The dissolution profiles observed for the above formulations showed that the drug release could not be controlled by a simple core till 12 hours though the hypromellose concentration was increased to 80-100mg/tablet. So in order to achieve the extended drug release the coating concept was employed. In order to control the initial burst release of highly soluble drug and extend the drug release from the system to 12 hours the unit operation of coating was employed using coating polymers like aqueous ethyl cellulose and hypromellose (HPMC E3 LV).

To build up coating 50:50 ratio of aqueous ethyl cellulose and Hypromellose (HPMC E3 LV).

Preparation of Coating Solution

Procedure

1. Weigh accurate quantity of HPMC E3 LV; dissolve in required quantity of purified water under stirring for 30min.
2. To the weighed quantity of aqueous ethyl cellulose dispersion add the solution of step 1, under stirring for 1hr to get uniform dispersion.

Calculations for control release coating

100gm of aqueous ethyl cellulose contains 25gms of solids i.e. equivalent to 18.8gms of Ethyl cellulose 20cps.

In formulation F7 the core tablets were coated with aqueous ethyl cellulose (6%) in order to extend the drug release by functional coating. The coated tablets were subjected to dissolution studies and the drug release profile was established for 12 hours.

The release showed that the drug release was highly retarded with the coating polymer aqueous ethyl cellulose.

The coating solution composition was prepared with 50:50 ratios of aqueous ethyl cellulose and HPMC E3 LV. During the coating process samples were collected at 2%, 3% and 4% coating build up and the formulations were designated as F8A, F8B and F8C. The coated tablets were kept for dissolution studies till 12 hours. At 2%-3% coating build up the drug release profiles were showed maximum drug release with in 10 hr. At 4% coating build up the drug release profile that was controlled the drug release up to 12 hr.

From the above results, all the parameters of tablets from various trial batch formulations were found to be within the limits of US Pharmacopeia.

STABILITY STUDIES

Experimental Study

Stability studies was conducted at 40ºC / 75% RH for about 2 months in stability chamber (MSN lab). Samples were collected and analyzed after 2nd month.

Sampling time points: Initial, 1month, 2month.

Evaluation parameters: Appearance of tablets, Assay and % drug dissolved.

Accelerated Stability Studies

Stability studies were conducted at 40ºC / 75% RH for about 2 months in stability chamber (thermo lab). Samples were collected and analyzed after 2nd month.

By comparing the initial values of Assay, and % CDR of F8C batch with their respective values analyzed after 2 months of stability studies, a very minute difference have been found between those values. Hence it was concluded that F8C was stable formulation.

Table No.1: List of materials selected for formulation development

S.No	Excipients	Category	Manufacturer
1	Tolmetin	API	MSN pharma
2	Lactose monohydrate	Filler	Meggle Wasserburg.
3	Micro crystalline cellulose	Disintegrant	Dow Chemicals
4	Povidone	Binder	ISP Pvt Ltd.
5	Hydroxy propyl methyl cellulose	Rate retarding polymer	M.B Sugars and pharmaceuticals
6	HEC	Rate retarding polymer	Signet Chemicals
7	Colloidal silicon dioxide	Glidant	Avionic Industries
8	Magnesium stearate	Lubricant	Ferro Corporation
9	Aqueous ethyl cellulose solution	Functional Coating agent	Colorcon Asia Pvt Ltd.
10	Purified water	Binder solvent	-----

Table No.2: Optimization of core tablets

S.No	Ingredients	Trial Batches (mg/Tablet)									
		Direct compression	Wet granulation	Polymer optimization				Coating optimization			
										F8	
Intra Granular		F1	F2	F3	F4	F5	F6	F7	F8 A	F8 B	F8 c
									2%	3%	4%
1	Tolmetin	600	600	600	600	600	600	600	600	600	600
2	Microcrystalline Cellulose	50	50	50	50	50	50	50	50	50	50
3	Lactose Monohydrate	120	120	120	120	120	120	120	120	120	120
4	Colloidal Silicon dioxide	3	3	3	3	3	3	3	3	3	3
Binder											
5	Polyvinyl pyrrolidone	15	15	15	15	15	15	15	15	15	15
Extra Granular											
6	HPMC K15M CR	50	50	--	--	80	100	80	80	80	80
7	HPMC K 100M CR	--	--	150	100	--	--	--	--	--	--
8	HEC	--	--	--	100	--	--	--	--	--	--
9	Colloidal Silicon dioxide	7	7	8	8	7	7	7	7	7	7
10	Magnesium Stearate	7	7	8	8	7	7	7	7	7	7
11	Aqueous ethyl cellulose solution	--	--	--	--	--	--	25.62	38.34	38.34	38.34
12	HPMC E3LV	--	--	--	--	--	--	--	25.56	25.56	25.56

Table No.3: Particle size analysis of Tolmetin

S.No	Mesh No	Pore size*	W_o	$W1$	$W1- W_o$	% Retained
1	#60	250 µm	345	345	0	0%
2	#80	180 µm	348.7	350.85	2.15	4.30%
3	#100	150 µm	335.8	344.9	4.55	9.10%
4	#140	106 µm	368.8	409.55	40.75	81.50%
5	#200	75 µm	329.5	331.35	1.85	3.70%
6	Blank	-	518.3	519	0.7	1.40%

* According to USP32

Table No.4: Spectrophotometric Data for the Estimation of Tolmetin in Ph 6.8 Buffer

S.No	Concentration(µg/ml)	Absorbance at 332nm
1	0	0
2	5	0.093
3	10	0.192
4	15	0.294
5	20	0.398
6	25	0.499
7	30	0.609
8	35	0.715
9	40	0.812

Table No.5: Drug-Excipients Compatibility Study

S.No	Name of the Excipient	Ratio of API: Excipient	Initial Observation	Final Observation 40ºC/75% RH			Conclusion
				1st Week	2nd Week	4th Week	
1	Tolmetin	1:0	White Colour	White Colour	White Colour	White Colour	Compatible
2	Drug + Lactose Monohydrate (Granulac 200)	1:1	White Colour	White Colour	White Colour	White Colour	Compatible
3	Drug + Micro crystalline cellulose	1:1	White Colour	White Colour	White Colour	White Colour	Compatible
4	Drug + Starch partially pre gelatinized (Starch 1500)	1:0.5	White Colour	White Colour	White Colour	White Colour	Compatible
5	Drug + Povidone (Plasdone K-29/32)	1:0.5	White Colour	White Colour	White Colour	White Colour	Compatible
6	Drug + Hypromellose (HPME K15M CR)	1:0.5	White Colour	White Colour	White Colour	White Colour	Compatible
7	Drug + Hypromellose (HPME K100M CR)	1:0.5	White Colour	White Colour	White Colour	White Colour	Compatible
8	Drug + HEC	1:0.5	White Colour	White Colour	White Colour	White Colour	Compatible
9	Drug + aqueous ethyl cellulose	1:0.5	Light yellow Colour	Light yellow Colour	Light yellow Colour	Light yellow Colour	Compatible
10	Drug+hypromellose(HPMCE3LV)	1:0.5	White Colour	White Colour	White Colour	White Colour	Compatible
11	Drug + Colloidal Silicondioxide (Aerosil 200)	1:0.1	White Colour	White Colour	White Colour	White Colour	Compatible
12	Drug + Magnesium Stearate	1:0.1	White Colour	White Colour	White Colour	White Colour	Compatible

Table No.6: Summary of Excipients Selection

S.No	Excipients	Category
1	Lactose monohydrate	Filler
2	Micro crystalline cellulose	Disintegrant
3	Povidone	Binder
4	Hydroxy propyl methyl cellulose	Rate retarding polymer
5	HEC	Rate retarding polymer
6	Colloidal silicon dioxide	Glidant
7	Magnesium stearate	Lubricant
8	Aqueous ethyl cellulose solution	Functional Coating agent
9	Purified water	Binder solvent

Table No.7: Evaluation of flow properties of blends of various trial batches were mean ± SD, n=3

S.No	Formulation code	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner's ratio
1	F1	43.91±1.09	0.49±0.012	0.63±0.062	20.87±2.225	1.16±0.018
2	F2	26.51±0.98	0.79±0.006	0.77±0.024	9.28±0.009	1.02±0.007
3	F3	28.56±1.32	0.66±0.002	0.74±0.165	9.02±0.009	1.17±0.155
4	F4	26.47±1.42	0.77±0.012	0.85±0.231	8.96±0.056	1.12±0.146
5	F5	27.41±1.59	0.73±0.011	0.69±0.013	8.82±0.156	1.09±0.017
6	F6	28.25±1.39	0.62±0.021	0.59±0.008	8.36±0.447	1.07±0.015
7	F7	28.34±0.32	0.66±0.008	0.74±0.012	7.91±0.124	1.79±0.003
8	F8A	29.92±1.18	0.69±0.088	0.76±0.022	8.20±0.098	1.03±0.156
9	F8B	29.83±1.70	0.61±0.014	0.65±0.007	8.48±0.089	1.89±0.001
10	F8C	28.34±0.32	0.66±0.008	0.74±0.012	7.91±0.124	1.79±0.003

Table No.8: Evaluation of Tolmetin Uncoated Tablets (F2- F6) Were Mean ± SD

S.No	Tests	Specifications	F2	F3	F4	F5	F6
1	Description	White colored oblong shaped uncoated tablets	complies	complies	complies	complies	complies
2	Average weight(g)	Varies(0.506-0.525)	0.510	0.5103	0.5144	0.5156	0.5181
3	Weight variation(n=20)	±5% from the average weight	+2.12-2.2	+2.3-2.4	+2.8-2.7	+3.7-2.6	+2.4-2.7
4	Thickness(mm)	6-6.4	6.15±0.14	6.18±0.29	6.17±0.18	6.10±0.15	6.22±0.3 4
5	Hardness(kp)	8-12	6.8±0.01	4.5±0.02	7.8±0.03	10±0.02	10.58±0.08
6	Friability (%w/w)	NMT 1%	Failed due to chipping	1.16±0.01	0.21±0.01	0.19±0.01	0.24±0.02
7	Disintegration time(min)	0-15	17	9	9.8	10.8	11.5
8	Assay (%)	----	99.15	98.99	98.89	99.22	98.51

Table No.9: Cumulative % Drug Release of Innovator, F2

Time	Innovator	F2
0	0	0
30min	2.7	19.7
1hr	5.7	28
2hr	20.5	40.6
3hr	31.9	59.5
4hr	42.1	69.4
6hr	76.3	88
8hr	88.1	97.5
12hr	98.7	100.5

Table No.10: Cumulative % Drug Release of Innovator, F3, F4, F5 and F6

S.No	Time	Innovator	F3	F4	F5	F6
1	0	0	0	0	0	0
2	30min	14.3	8.3	7.9	11.2	13.6
3	1hr	25.1	13.3	13.5	23.1	19.4
4	2hr	54.3	38.3	40.5	34.5	29.4
5	3hr	68.5	52.1	59.6	44.1	40
6	4hr	83.7	71.9	74.7	56.8	46.3
7	6hr	98.1	89.6	87.8	69.3	60

Table No.11: Evaluation of Tolmetin Coated Tablets

S.No	Tests	specification	F7	F8A	F8B	F8C
1	Description	White colored oblong shaped enteric coated tablets	complies	complies	complies	complies
2	Average weight(g)	Varies(0.530-0.59)	0.5322	0.5433	0.5528	0.5682
3	Weight variation(n=20)	± 5% from the average weight	+2.4-3.1	+2.7-2.4	+2.0-2.6	+3.3-3.2
4	Thickness(mm)	6-8	7.15±0.26	7.18±0.49	7.19±0.52	7.18±0.28
5	Hardness (kp)	10-15	11.7±0.02	12.5±0.02	13.1±0.2	14.0±0.01
6	Friability (%w/w)	NMT%	0.22±0.01	0.24±0.01	0.24±0.06	0.39±0.01
7	Disintegration time (min)	0-15	7	8	8.5	10
8	Coating uniformity (%)	---	3.15	3.29	3.49	3.52
9	Coating process uniformity (%)	---	86.19	88.36	84.82	82.49
10	%LOD	---	2.32	2.98	3.12	3.98
11.	Assay (%)	---	100.12	99.21	98.32	99.2

Table No.12: Cumulative % Drug Release of Innovator, F7

S.No	Time	Innovator	F7
1	0	0	0
2	30min	14.3	1.1
3	1hr	25.1	5.5
4	2hr	54.3	7.5
5	3hr	68.5	12
6	4hr	83.7	24.8
7	6hr	98.1	30.2

Coating Calculations

S.No	Ratio	aqueous ethyl cellulose	HPMC E3 LV
1	50:50	100gm	18.8gm

Table No.13: Cumulative % Drug Release of Innovator, F8A, F8B and F8C

S.No	Time	Innovator	F8		
			F8A	F8B	F8C
1	0	0	0	0	0
2	30min	14.3	6.3	6.1	2.1
3	1hr	25.1	18.7	17.3	5.2
4	2hr	54.3	30.5	29.5	14.4
5	3hr	68.5	42.8	41.7	24.1
6	4hr	83.7	72.3	59.8	35.5
7	6hr	98.1	89.3	76.5	48.5
8	8hr	101.0	99.9	94.1	70.7
9	10hr	101	100.3	99.3	88.8
10	12hr	101	101.2	100	100.01

After 1st and 2nd Month

Table No.14: Physical evaluation for stability studies of optimized formulations

S.No		Initial	40^{0}C / 75% RH
1	Color	Light yellow	Light yellow
2	Surface	Smooth	Smooth
3	Assay	99.12%	98.55%

Table No.15: Cumulative Percentage release of stability studies of optimized formulation (F8C) at 40^{0}C / 75% RH For 1st and 2nd month

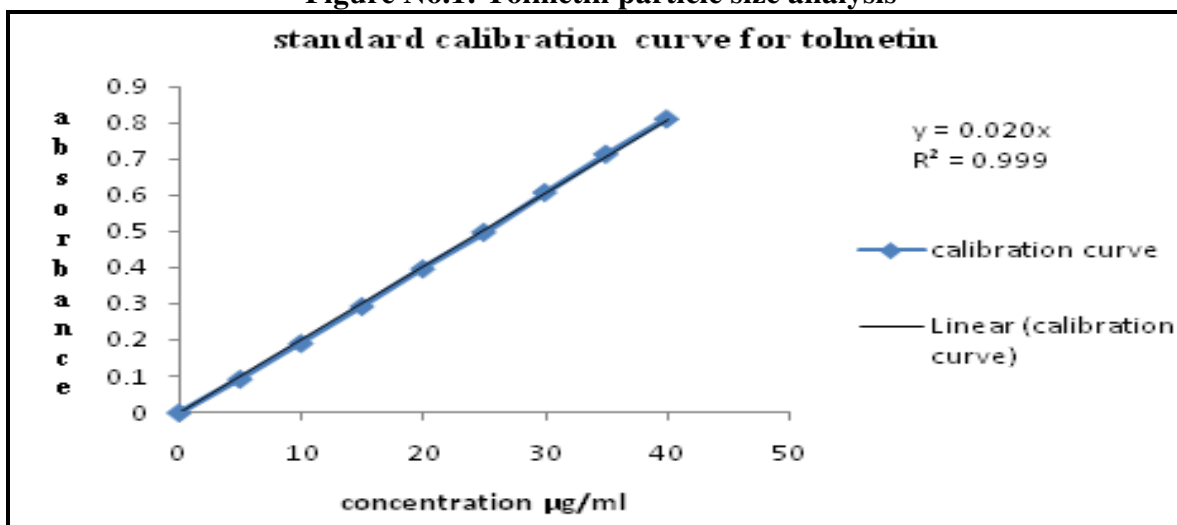| Time	F16C		
	Initial	1st Month	2nd Month
0	0	0	0
0.5	2.1	2.78	6.3
1	5.2	6.2	7.3
2	14.4	15.45	16.5
3	24.1	25.1	29.7
4	35.5	37.5	39.8
6	48.5	50.5	46.5
8	70.7	67.7	74.1
10	88.8	87.8	89.3
12	100.01	100.01	100
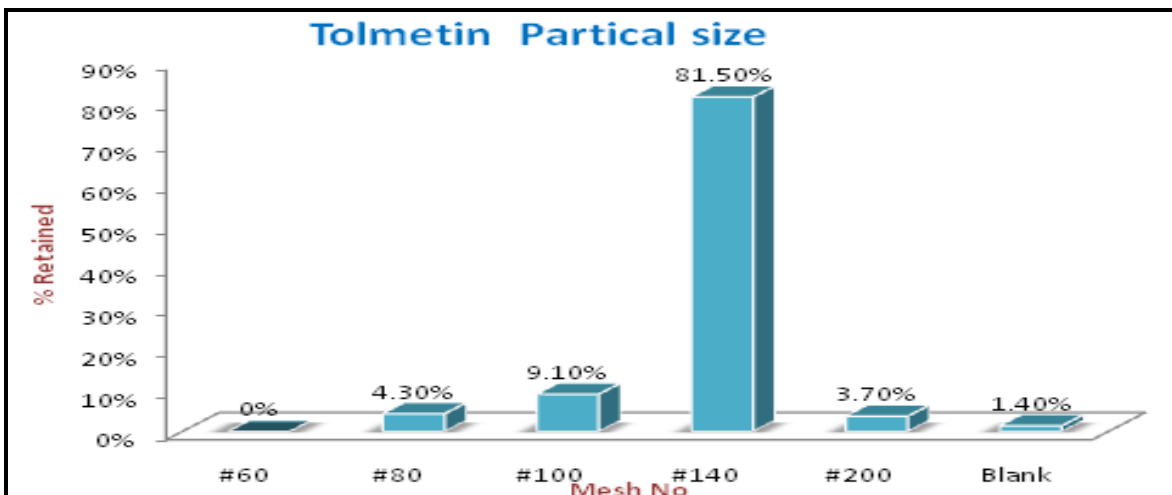
Figure No.1: Tolmetin particle size analysis

Figure No.2: Standard calibration Curve of Tolmetin in Ph 6.8 Buffer
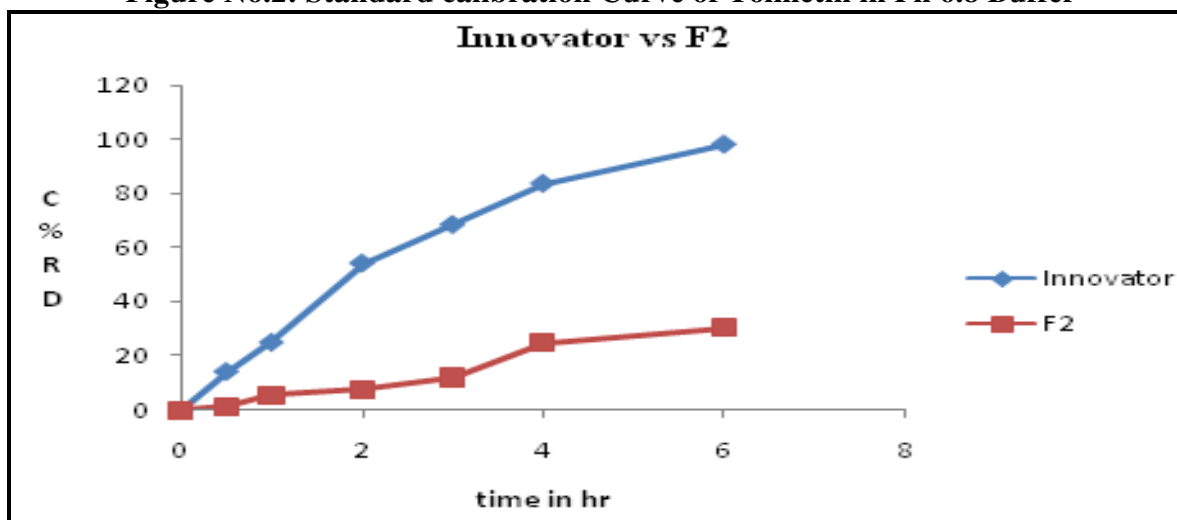

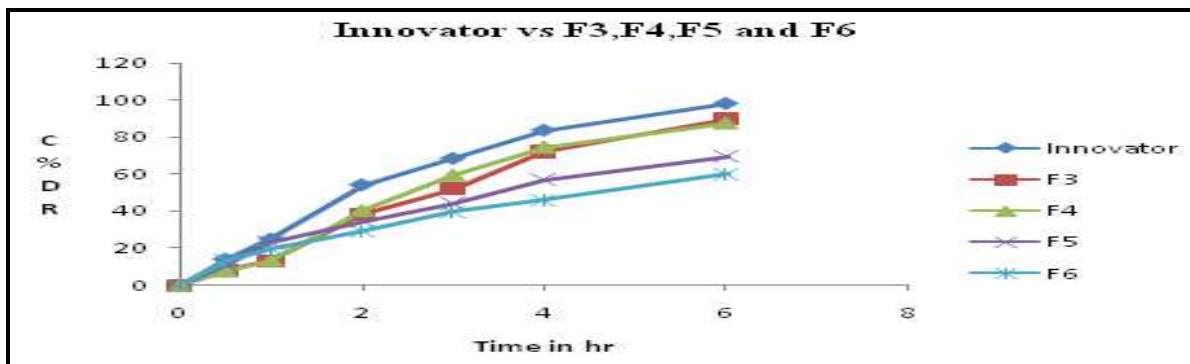**Figure No.3: Comparison of Cumulative % Drug Release F2 with Innovator**

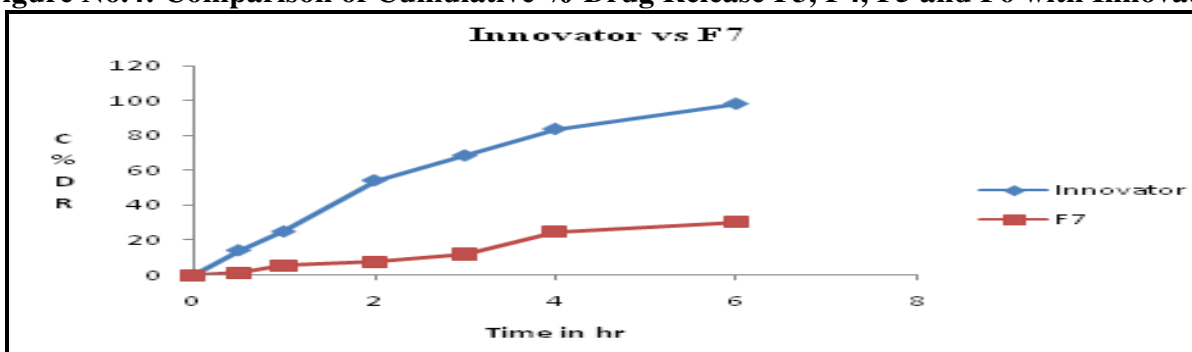**Figure No.4: Comparison of Cumulative % Drug Release F3, F4, F5 and F6 with Innovator**

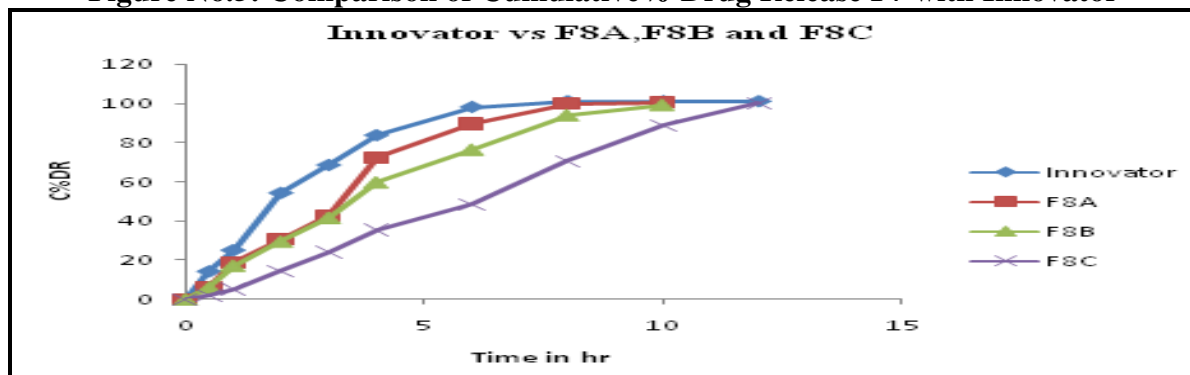**Figure No.5: Comparison of Cumulative% Drug Release F7 with Innovator**

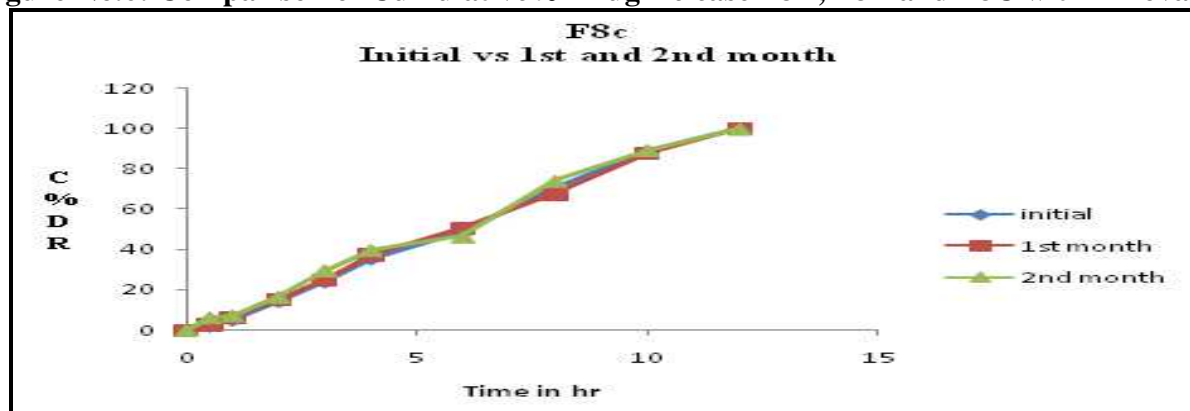**Figure No.6: Comparison of Cumulative% Drug Release F8A, F8B and F8C with Innovator**

Figure No.7: Dissolution profiles of initial, 1ˢᵗand 2nd month stability samples at 40⁰C / 75% RH

CONCLUSION

The Present study was undertaken with an aim to formulate and evaluate Tolmetin extended release tablets, mainly used for the treatment of muscle-skeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, rheumatoid arthritis and acute gout. Experiment was performed by using both dry and wet granulation techniques based on the flow properties of API. In order to increase the flow property of the tablets, wet granulation was chosen for further formulation and found to be satisfactory. During Development of formula, in-process tests such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose were evaluated for granules and hardness, friability, weight variation, thickness and disintegration were evaluated for the core tablets. Core tablets were coated with coating suspension. Materials used for coating were shown in the Table No.2. Finished products were evaluated for hardness, friability, weight variation, thickness, disintegration, dissolution and drug content. The coated tablets of E3 formulations were packed in HDPE containers and stability studies performed at 45°C /75% RH for 2 months. Stability samples were evaluated initially and after 2 months. The results were compared with the pre-determined specifications. All the results were found to be satisfactory.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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