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Preface

We would like to present, with great pleasure, the inaugural volume-6, Issue-8, August 2020, of a scholarly journal, *International Journal of Engineering Research & Science*. This journal is part of the AD Publications series *in the field of Engineering, Mathematics, Physics, Chemistry and science Research Development*, and is devoted to the gamut of Engineering and Science issues, from theoretical aspects to application-dependent studies and the validation of emerging technologies.

This journal was envisioned and founded to represent the growing needs of Engineering and Science as an emerging and increasingly vital field, now widely recognized as an integral part of scientific and technical investigations. Its mission is to become a voice of the Engineering and Science community, addressing researchers and practitioners in below areas

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Algorithm and Computational Complexity	Artificial Intelligence
Electronics & Communication Engineering	Image Processing
Information Retrieval	Low Power VLSI Design
Neural Networks	Plastic Engineering

Each article in this issue provides an example of a concrete industrial application or a case study of the presented methodology to amplify the impact of the contribution. We are very thankful to everybody within that community who supported the idea of creating a new Research with IJOER. We are certain that this issue will be followed by many others, reporting new developments in the Engineering and Science field. This issue would not have been possible without the great support of the Reviewer, Editorial Board members and also with our Advisory Board Members, and we would like to express our sincere thanks to all of them. We would also like to express our gratitude to the editorial staff of AD Publications, who supported us at every stage of the project. It is our hope that this fine collection of articles will be a valuable resource for *IJOER* readers and will stimulate further research into the vibrant area of Engineering and Science Research.

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In-Wheel Motor Transmission System in Electric Vehicle

Anindya Anupam Parida

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Abstract— *Electric vehicle is the alternative, efficient and eco friendly in the future automobile industry. In today's world due to depreciation of the fossil fuels rapidly, engineers have found the other mode of vehicle movement.ie- moving the car or a vehicle by the mode of electric motor. The end of the engines powered by fossil fuels and entering to the new era of electric automobile by 2075 almost 95% of the fossil fuel content and production from the earth will get over. There are electric vehicles like Tesla automobile and some other companies like Mahindra etc have started production of electric vehicles and the vehicle is powered by AC Induction motor, BLDC motor etc by using shafts and cv axle for transmission of power generated. Here this research paper is about the implementation of in-wheel electric motor, construction, mechanism and working of alternative design of 3 phase ac induction 4 pole motor with figures and tables.*

Keywords— electric motor, efficiency, transmission system, transmission.

I. INTRODUCTION

In 1887, AC Induction motor was invented by Nikola Tesla and Galileo Ferraris, known by Tesla motor. Ac induction motor is electrical device which works on the principle of electric magnetic induction, in which it consists mainly two parts stator and a rotor, and stator remains fixed and rotor rotates inside the stator, where both have the windings named stator winding and rotor winding . when ac current is supplied to the motor , magnetic field is produced which helps rotor to rotate in result rotates the shaft and wheel rotates .There are various types of ac induction motors like 2 phase induction motor, 3 phase induction motor. Tesla electric automobile which is the most efficient and fastest car in the world uses 3-phase 4 pole AC induction motor , whose wires are connected in star connection as shown in below fig.1.

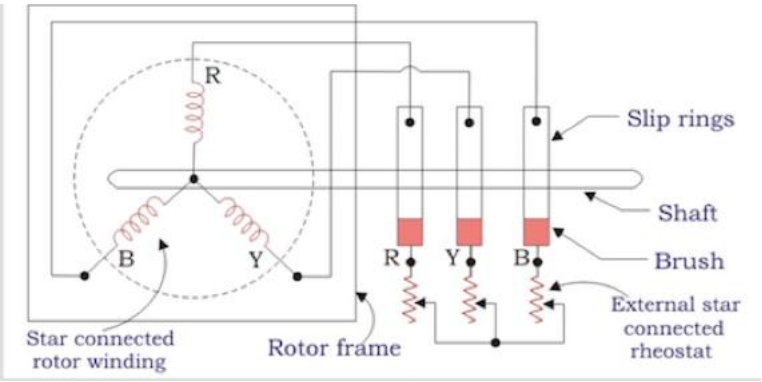

FIGURE 1: Star Connection in AC Motor

As we need more torque so for that we know the condition that less is the number of poles more is the torque produced, as per research its found that 3 phase 4 pole induction motor is the most efficient electric motor but as it uses cv axle for the transmission of torque to the wheels there is loss and efficiency is decreased. We are in a rapid developing technological world new technology and inventions we come across frequently. Not only for the minimizing the losses and increasing the torque but also for the new technological method for which future electric vehicle can be taken to the next level of automobile industry.

II. THEORY

The concept behind this new technology "direct wheel-motor transmission system in electric vehicle", we have various and enough ways to propel a car or an vehicle but the methods of propelling used before was using SI Engine (spark ignition or petrol engine) or CI Engine (compression ignition or diesel engine) where the car consists of transmission system which consists of Engine, Gear box or transmission, Clutch, connecting shaft (from engine to differentials), Differentials, Cv axle. This is the whole method of transmitting power from the engine to the wheels in form of torque. If a vehicle consists of so much of components then the empty space in the vehicle decreases and most important there are many losses due to this kind of transmission, and engineers cannot fit the engine directly in contact or inside the wheel as the space inside the rims of the

wheel is too less and engine isn't that compact to fit in. Now the new era is coming i.e. Electric vehicle generation, where electric motors like Ac motor or BLDC motors, till date since the electric cars are made electric motors are placed between the two wheels from where power is transmitted to the wheels via connecting shaft or cv axle. Let's take an example of world's first and most advanced electric car.ie-Tesla automotive. If we take example of Tesla roadster it's the world's fastest car it uses THREE-AC 3 phase 4 pole induction motors it's an all wheel drive as power is transmitted to all of the wheels. Motors are such things which can be made more powerful and more compact. In below fig. 2, we can see the how Tesla incorporates its motors in its car.

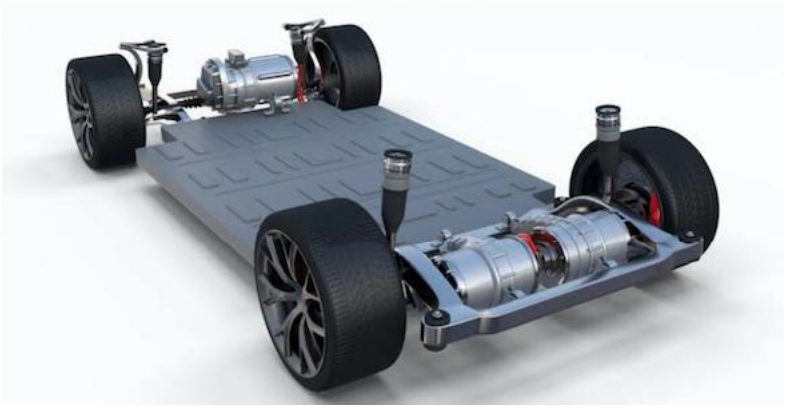

FIGURE 2: Motors incorporated in Tesla Roadster

III. EFFECTS & PROBLEM OF USING THE ELECTRIC MOTORS IN BETWEEN THE TWO WHEELS

There are many effects which occur to a vehicle. This kind of transmission system in the vehicle occupies most of the area of the car base and less empty space is left. By using cv axle to transmit the power it restricts the turning radius of the wheel. Power transmission in this method there are many losses like mechanical losses, frictional losses, less efficiency.

IV. MY PROPOSAL FOR THE NEW TECHNOLOGY AND SOLVING THE PROBLEMS

My proposal for the new technology is "IN-WHEEL MOTOR TRANSMISSION SYSTEM" to be used in electric vehicle. On going to the explanation part of this technology:

4.1 In-Wheel Motor Technology

This technology has not been used by any automobile manufacturer company till date. Basically in wheel motor means motors are placed inside the rims of the wheels. There will be no cv axle or connecting shaft be used for transmitting the power to the wheels. This hypothesis is given by a small company know as protean but their research is not competed yet, it's under process and they have used dc motor. Myself I have a motor of higher torque, I have made use of 3 phase ac induction motor as its much more efficient than that of dc motor whose power, torque, weight etc is given in below table.4.1.1 and that's of 3 phase Ac induction 4 pole motor which is placed inside the wheels. The values stated below for the AC induction motor is for single motor, for more power of the car we can use 3-4 motors, 1 motor in each wheel, simultaneously if we use 2 motors at the back it will act as rear wheel drive, if 2 is used in the front it will act as front wheel drive and if we use 4 motors in a car then it acts as all wheel drive (which makes the car very powerful).

TABLE 1
SPECIFICATION OF PROPOSED 3 PHASE INDUCTION MOTOR

Parameter	Details
Added weight	34 kg
Peak Torque	1500 Nm
Continuous Torque	650 Nm
Top Speed [At nominal Voltage]	1480 rpm
Peak Power [At nominal Voltage]	110 kW
Continuous Power [At nominal Voltage]	77 kW (Liquid cooling)

The construction of the motor is in such a way that it will exactly fit into the rims. While the motor having the screws coming in outward direction so as to get fit into the wheels depending on the no. Of lugs used in the car if the vehicle is of less power

and small then 4 lugs are used in wheels and if the vehicle is having higher power like sedans and heavy vehicle it can go from 5 lugs to 6 lugs.

4.2 Author's technology construction and working

Generally ac motors are of cylindrical in shape but our shape of ac motor is circular in shape with some width exactly to that of rims of wheels. This motor consists of all the components same as that of other ac motors like stator, stator bracket, rotor, rotor bracket, inverter, bearing , motor outer case, front end bell and rear end bell, power electronics, brake disc, brake calliper. The fitting of motor in wheels can be seen in below figure 3.

FIGURE 3: Fitting of Motor wheels

Basically this motor mainly consists of a stator and a rotor where rotor is inside the stator and an inverter connected to the stator. With the motor from the outer casing of motor suspension is attached which is attached to the chassis of the vehicle. Moreover all the attachment system is fully different in this system. In simpler words we can say here the outer casing of the motor acts as a hub with screws to hold the wheel (the fig shown above wheel is of 5 lugs), for steering control, steering control rods are connected above the suspension system with the supporting system is given for the motor and wheel. This system removes the restrictions to the turning radius of a vehicle. Steering arms and steering system can be seen in the below fig.4 and fig.5.

FIGURE 4: (Rear view)

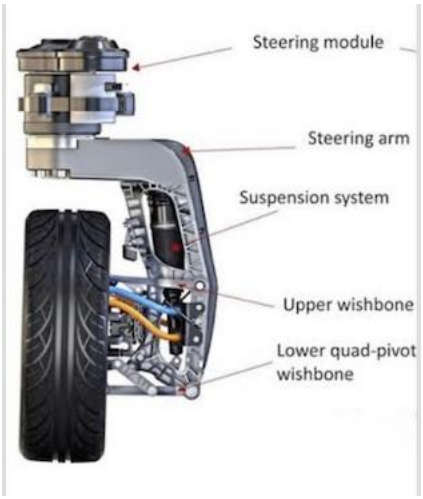

FIGURE 5: (side view)

As we can see in the above fig. From the steering module, steering connecting rods will get connected and then to the steering wheel and some important parts which gives support to the wheels and motor.

This new technology which will be very beneficial in the future and I will be trying it on my project sports car in progress.

Below figures we can see the organic chassis structure made in solid works platform and the real ongoing project sports car where it will be applied later.

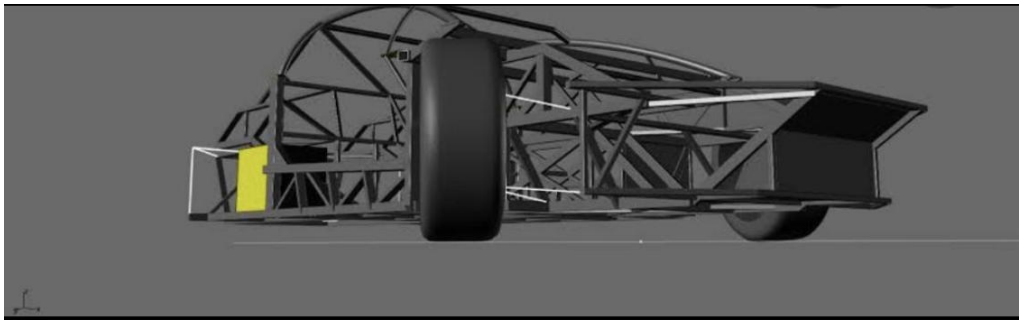

FIGURE 6: Organic Chassis of my Sports Car (Drawn in Solid Works)

FIGURE 7: Organic Chassis and Sports Car in Progress in Real.

4.3 Advantages of in-wheel motor transmission system

There are many advantages of behind this invention. The most important point is these systems are as stated below:

1) As there is no restrictions in the turning radius so the wheel can turn upto 180 degrees, in that case if all 4 wheels turn through 180 degrees then by standing in one position without any extra area a vehicle can turn directly through 180 degree or 360 degree, which will be very helpful where there will be less place to take turn and parking's, etc.

2) Direct transmission of power from the motor to the wheel in form of torque (2*pi*N/60), decreases the losses as direct attachment is there in result increases the torque.

3) Free space in vehicle increases as there is no components in the chassis base rather than batteries. We get extra free spaces.

V. CONCLUSION

This innovation will be proved very useful in the near future if this system will be installed in the electric cars and other vehicles and lots of problems will be solved by this. I am personally going to apply this on my experimental car which I am making can be seen in the fig. 7.

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Design, Formulation Development and Evaluation of Matrix Tablet Containing Labetalol HCL

Dileep Kumar Awasthi[1*], Sangamesh B. Puranik[2], Rohit Saraswat[3], Mahesh Kumar Jhajharia[4], Prashant Sharma[5]

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Abstract— *The objective of present work was to design and develop sustained release matrix tablets of anti-hypertensive drug Labetalol hydrochloride. Hydroxypropyl methyl cellulose K15, Sodium CMC, Xanthan gum and Tamarind seed polysaccharide used as a rate retarding polymer. Whereas Polyvinyl Pyrrolidone and Microcrystalline cellulose are used as granulating agent and diluent. The influence of variable concentration of polymers on the release rate of drug was investigated. The results of the present work point out that the rate of Labetalol hydrochloride release from polymers like Hydroxypropyl methyl cellulose K15, Sodium CMC, Xanthan gum and Tamarind seed polysaccharide are mainly controlled by the drug–polymer ratio. The prepared sustained release matrix tablets were evaluated for various parameters like hardness, friability, uniformity of weight, uniformity of drug content and in vitro drug release studies.*

Keywords— Hydroxypropyl methyl cellulose K15, Sodium CMC, Xanthan gum and Tamarind seed polysaccharide, Sustained-release, Labetalol hydrochloride Formulation.

I. INTRODUCTION

Sustained release system includes any drug delivery system that "achieves slow release of drug over an extended period of time." The term sustained release has become associated with those systems from which therapeutic agent may be automatically delivered over a long period of time. A simple dosing scheme with a once or twice daily administration of the antihypertensive agent is known to increase patient compliance. For this reason, the pharmaceutical industry is intensively searching for longer-acting antihypertensive drugs, either by the development of novel agents with a longer elimination half life, or by the improvement of the dosage form of existing shorter acting compounds, so that plasma concentrations compatible with a blood pressure lowering activity are maintained during the whole day. Sustained drug delivery has been introduced to overcome the drawback of fluctuating drug level associated with conventional dosage form [1-3].

The goal in designing oral sustained or controlled delivery is to reduce the frequency of the dosing or to increase effectiveness of the drug by localizing at the site of action, reducing the dose required or provide uniform drug delivery, thereby also improving patient compliance. Controlled or sustained release dosage forms provide a better control drug levels, less dosage frequency, less than effects, increased efficiency and constant delivery [4].

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of sustained release drug delivery system like application of different polymers to achieve sustained delivery that could revolutionize method of medication and provide a number of therapeutic benefits. To fabricate matrix tablet of Labetalol HCl using polymers like Hydroxypropylmethylcellulose (HPMC), Sodium CMC, Xanthan gum and Tamarind seed polysaccharide (carried out the Isolation and Extraction of Tamarind seeds polysaccharide from tamarind husk kernels).

II. MATERIALS & METHODS:

Labetalol hydrochloride was obtained as a gift sample from Yarrow chem. distributor, Mumbai and ingredients like HPMC K 15, Sodium CMC, Microcrystalline Cellulose, and Talc, obtained from loba chemicals Mumbai. Tamarind seed polysaccharide is used.

2.1 Preparation of Matrix Tablets of Labetalol Hydrochloride:

In the present work, wet granulation method has been used to prepare matrix tablets of Labetalol hydrochloride and the polymer used is:

Hydrophilic swellable polymer i.e., hydroxypropyl methyl cellulose with grade K15. Sodium CMC Xanthan gum TSP (Starch).

2.2 Diluents (bulking agent or compression vehicles) used are

- Microcrystalline cellulose
- Binder**:** Polyvinyl pyrrolidone K30 (PVPK30) in water.
- Lubricant**:** Magnesium stearate Glidant**:** Talc

2.3 Method:

In the present work, drug with different polymer in their variable concentration is used to give a drug- polymer proportion of 1:0.5, 1:0.75 and 1:1 for the preparation of matrix tablet. Among the three drug polymer ratios studied drug-polymer ratio 1:1 released approximately 90% of the drug in 11.5 hours.

2.3.1 Procedure for Preparation of Matrix Tablets

Matrix tablets were prepared by wet granulation method. The composition with respect to drug- polymer ratio 1:0.5, 1:0.75 and 1:1 was selected. Weighed all the ingredients accurately. Drug, Polymer and diluents were mixed in a poly bag and the mixture was passed through a mesh No. 44.Granulation was done with a solution of PVP K30 in sufficient quantity of distilled water. The wet mass was passed through mesh No. 22 to get granule of desired size. The wet granules were dried at 50°C for about 2 hours. The dried granules were seized by a mesh No. 20 and mixed with magnesium stearate and talc. Granules thus obtained weighing equivalent to required weight were compressed into tablets by using 8mm flat round punches on a single punch sixteen station Cadmach tablet machine.

TABLE 1
FORMULATION CHART OF LABETALOL HCL MATRIX TABLET

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Labetalol HCl	100	100	100	100	100	100	100	100	100	100	100	100
HPMC K 15	50	75	100	-	-	-	-	-	-	-	-	-
Sodium CMC	-	-	-	50	75	100	-	-	-	-	-	-
Xanthan gum	-	-	-	-	-	-	50	75	100	-	-	-
TSP(Starch)	-	-	-	-	-	-	-	-	-	50	75	100
Microcrystalline cellulose	128.85	103.85	78.85	128.85	103.85	78.85	128.85	103.85	78.85	128.85	103.85	78.85
PVP K30	15	15	15	15	15	15	15	15	15	15	15	15
Magnesium stearate	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Talc	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Total weight (mg)	300	300	300	300	300	300	300	300	300	300	300	300

III. RESULT AND DISCUSSION:

3.1 Preformulation study of Labetalol HCl:-

3.1.1 Description

Test	Specification	Result
Description	White crystalline powder	White crystalline powder.

3.1.2 Solubility

Parameter	1 Trial	2 Trial	3Trial	Mean
Solubility* (mg/ml)	20	19.5	20.5	20

Solubility in water at $25^{O}C$

3.1.3 Melting point

3.1.3.1 Melting point of Labetalol HCl was found to be 1950c

Evaluation of Formulation Parameters:

Evaluation was divided in mainly

- Pre-compression Parameters.
- Post-compression Parameters.

3.2 Precompression Study

TABLE 2
RESULTS OF FLOW PROPERTIES

BATCH	ANGLE OF REPOSE(º)	BULK DENSITY (gm/ml)	TAPPED DENSITY (gm/)	COMPRESS-BILITY INDEX	HAUSNER'S RATIO
F1	24.6	0.537	0.610	12.23	1.13
F2	23.7	0.524	0.601	12.83	1.14
F3	24.7	0.541	0.626	13.55	1.15
F4	24.8	0.560	0.630	11.55	1.12
F5	23.5	0.580	0.658	11.85	1.13
F6	24.0	0.579	0.670	12.18	1.15
F7	23.5	0.565	0.637	12.80	1.12
F8	22.5	0.540	0.626	11.95	1.15
F9	23.6	0.559	0.631	12.63	1.12
F10	22.4	0.584	0.659	12.45	1.12
F11	25.2	0.545	0.625	11.82	1.14
F12	24.2	0.572	0.664	13.15	1.16

The formulated granules were characterized with respect to angle of repose, bulk density and tapped density. All granules from all formulation show excellent flow property.

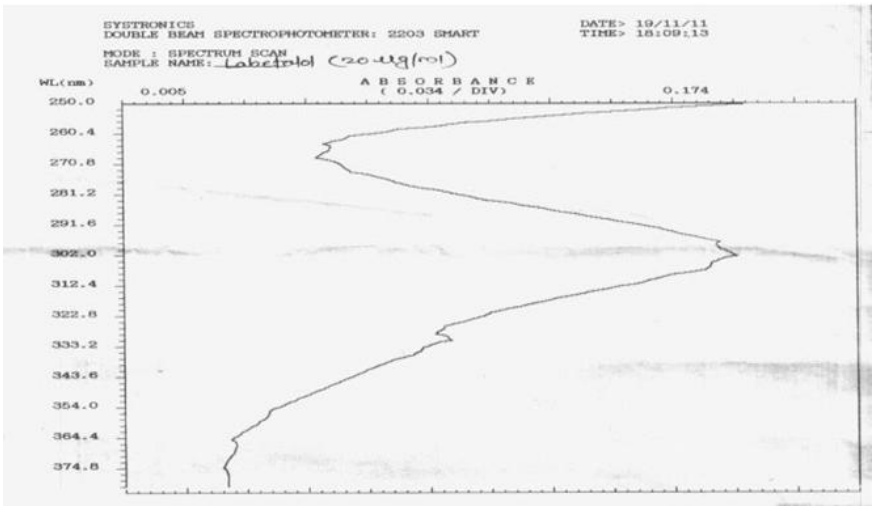


FIGURE 1: UV spectra of Labetalol HCl

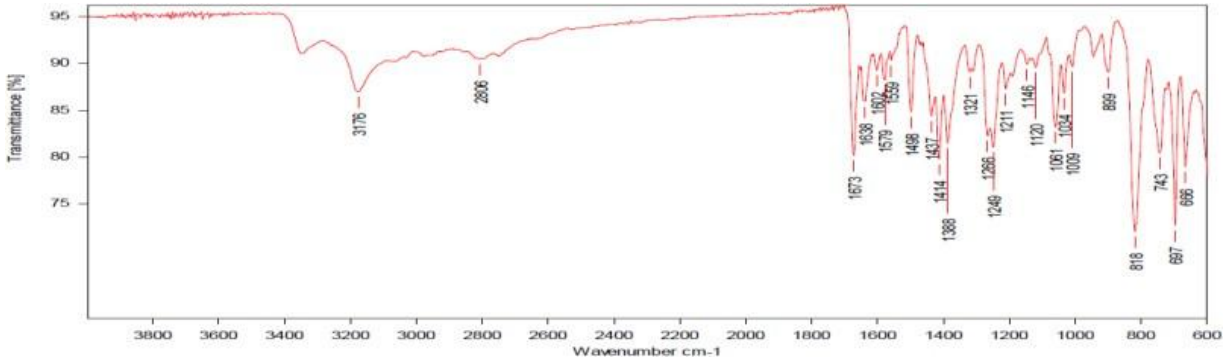


FIGURE 2: IR spectra of Labetalol HCl

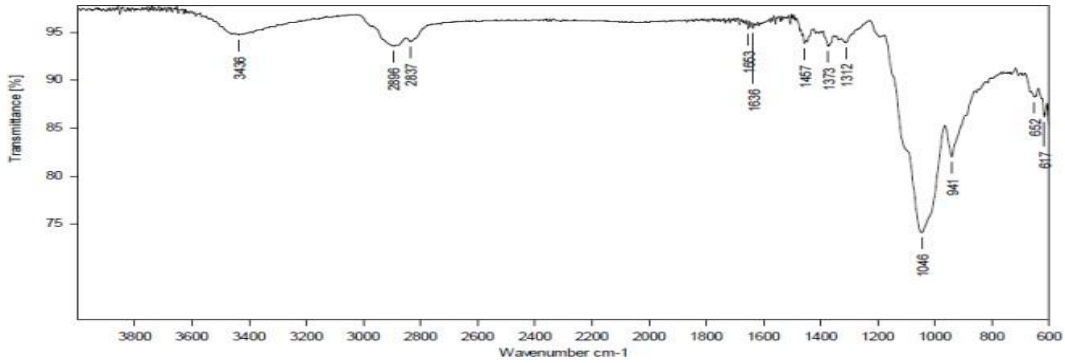


FIGURE 3: IR spectra of HPMC K 15

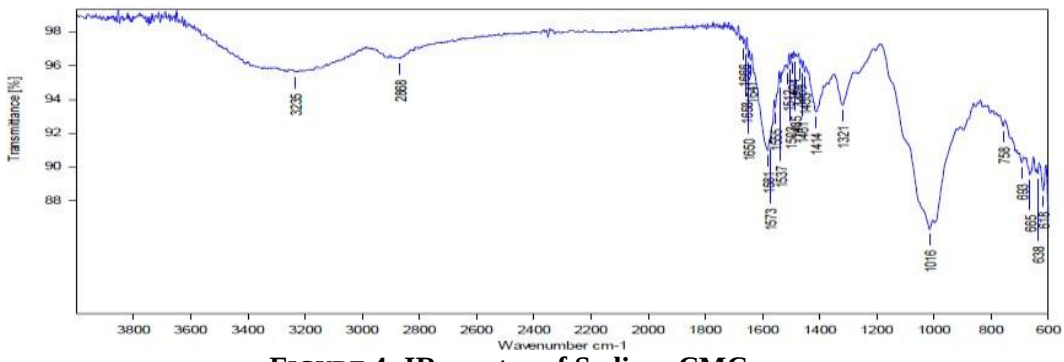


FIGURE 4: IR spectra of Sodium CMC

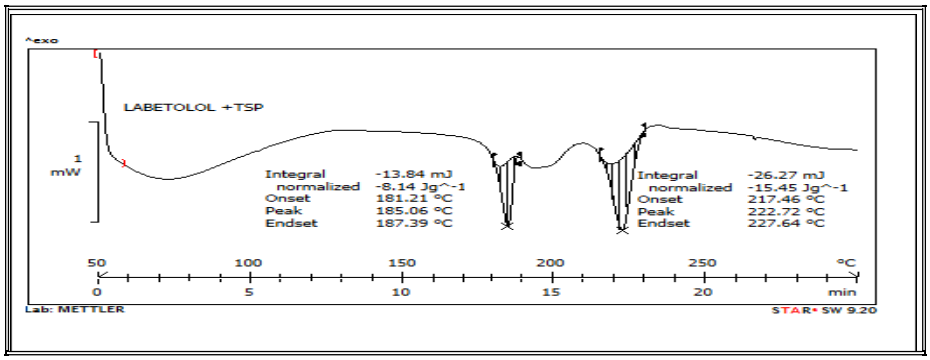


FIGURE 5: DSC SPECTRA OF LABETALOL + TAMARIND SEED POLYSACCHARIDE

TABLE 3
EVALUATION PARAMETERS OF FORMULATIONS

Formulation code	Evaluation parameter				
	Thickness ± S.D. (mm) (n = 5)	Hardness ± S.D. (kg/cm^2) (n = 5)	Friability (%)	Average weight variation (n=20)	Drug content (%)
F1	4.64±0.13	5.86±0.21	0.03	310±1.153	99.24
F2	4.55±0.11	5.74±0.41	0.07	295±2.111	95.41
F3	4.62±0.23	5.72±0.25	0.11	305±2.172	99.5
F4	4.52±0.15	5.82±0.25	0.63	310±1.183	96.87
F5	4.53±0.27	5.68±0.13	0.18	310±2.211	97.71
F6	4.44±0.19	5.66±0.23	0.21	290±1.121	98.47
F7	4.52±0.16	5.96±0.28	0.29	310±3.189	96.45
F8	4.53±0.19	5.44±0.23	0.17	290±1.198	98.98
F9	4.56±0.22	5.74±0.11	0.29	295±1.143	95.87
F10	4.65±0.21	5.62±0.19	0.27	290±0.102	97.33
F11	4.53±0.23	5.70±0.15	0.25	310±3.172	98.41
F12	4.43±0.21	5.72±0.23	0.67	290±2.173	97.07

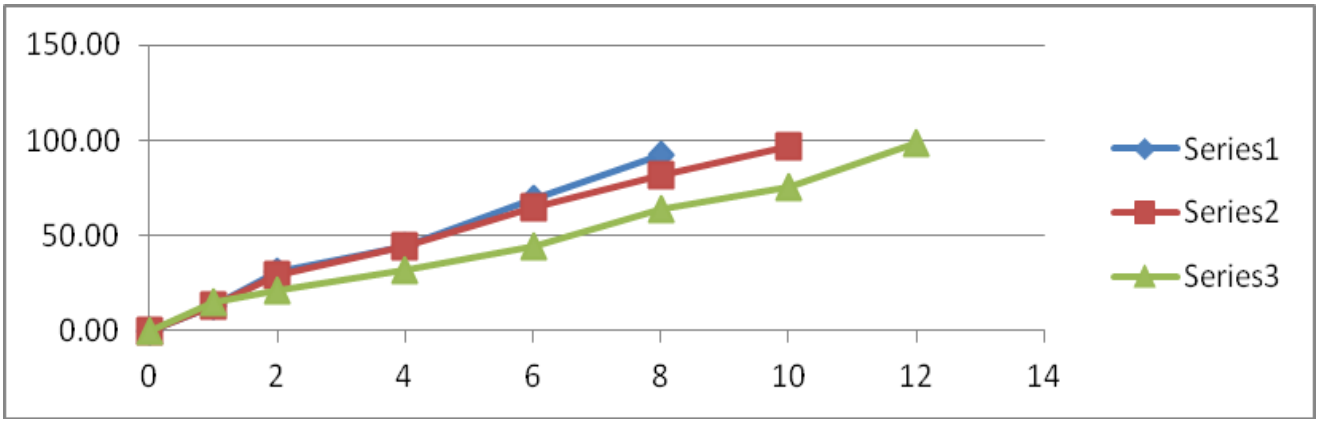
3.3 *In vitro* drug release of Labetalol HCl through HPMC K 15

TABLE 4
***IN VITRO* RELEASE PROFILE OF FORMULATION F1 &F2**

Time	F1					F2				
	Concentration of Drug (mg)		Cumulative loss	Cumulative drug release*		Concentration of drug (mg)		Cumulative loss	Cumulative drug release *	
	5ml	900ml	Mg	Mg	%	5ml	900ml	mg	mg	%
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.07	13.32	0.00	13.32	13.32	0.07	13.20	0.00	13.20	13.20
2	0.17	31.44	0.07	31.51	31.51	0.16	29.64	0.07	29.71	29.71
4	0.25	44.46	0.25	44.71	44.71	0.25	44.46	0.24	44.70	44.70
6	0.38	68.52	0.50	69.02	69.02	0.36	64.26	0.49	64.75	64.75
8	0.51	91.08	0.88	91.96	91.96	0.45	81.12	0.84	81.96	81.96
10	-	-	-	-	-	0.53	95.52	1.29	96.81	96.81

TABLE 5
***IN VITRO* RELEASE PROFILE OF FORMULATION F_3**

Time	F3				
	concentration of Drug (mg)		cumulative loss	Cumulative drug release	
	5ml	900ml	mg	Mg	%
0	0	0	0	0	0
1	0.09	15.54	0.00	15.54	15.54
2	0.12	21.48	0.09	21.57	21.57
4	0.18	31.98	0.21	32.19	32.19
6	0.24	43.86	0.38	44.24	44.24
8	0.35	63.36	0.63	63.99	63.99
10	0.42	74.88	0.98	75.86	75.86
12	0.54	96.78	1.40	98.18	98.18



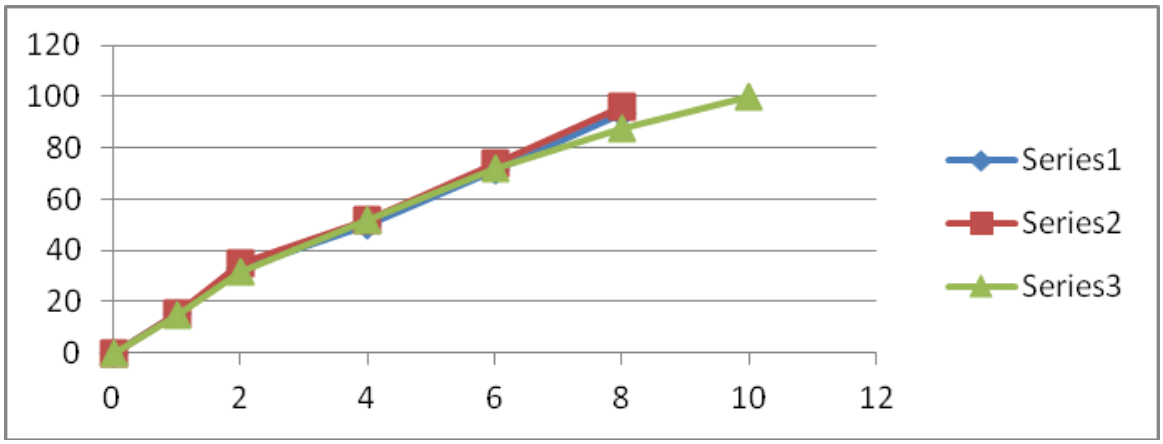
GRAPH 1: In vitro drug release of Labetalol HCl through HPMC K 15 (F1, F2, F3)

TABLE 6
***IN VITRO* DRUG RELEASE OF LABETALOL HCL THROUGH SODIUM CMC**

Time	F4					F5				
	Concentration of Drug (mg)		Cumulative loss	Cumulative drug release*		Concentration of drug (mg)		Cumulative loss	Cumulative drug release *	
	5ml	900ml	mg	mg	%	5ml	900ml	mg	mg	%
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.09	13.32	0.00	15.48	15.48	0.09	15.48	0.00	15.48	15.48
2	0.18	31.44	0.09	32.97	32.97	0.19	34.98	0.09	35.07	35.07
4	0.28	44.46	0.27	50.07	50.07	0.29	51.30	0.28	51.58	51.58
6	0.39	68.52	0.55	71.47	71.47	0.41	73.50	0.57	74.07	74.07
8	0.51	92.52	0.93	93.45	93.45	0.53	94.86	0.97	95.13	95.13

TABLE 7
IN VITRO RELEASE PROFILE OF FORMULATION F_6

Time	F6				
	concentration of Drug (mg)		cumulative loss	Cumulative drug release	
	5ml	900ml	mg	mg	%
0	0	0	0	0	0
1	0.08	14.94	0.00	14.94	14.94
2	0.17	31.38	0.08	31.46	31.46
4	0.29	51.42	0.26	51.68	51.68
6	0.40	71.16	0.54	71.70	71.70
8	0.48	86.46	0.94	87.40	87.40
10	0.55	98.34	1.42	99.76	99.76



GRAPH NO. 2 *In vitro* drug release of Labetalol through Sodium CMC (F4, F5, F6)

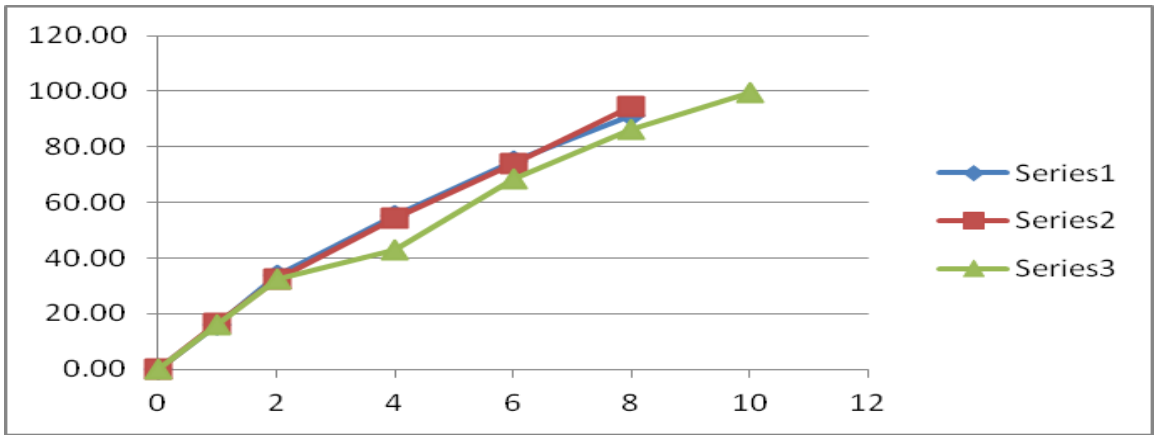
3.4 *In vitro* drug release of Labetalol through Xanthan gum

TABLE 8
***IN VITRO* RELEASE PROFILE OF FORMULATION F_7 & F_8**

Time	F7					F8				
	Concentration of Drug (mg)		Cumulative loss	Cumulative drug release*		Concentration of drug (mg)		Cumulative loss	Cumulative drug release *	
	5ml	900ml	mg	mg	%	5ml	900ml	mg	mg	%
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.09	16.26	0.00	16.26	16.26	0.09	16.56	0.00	16.56	16.56
2	0.19	33.78	0.09	33.87	33.87	0.18	32.28	0.09	32.37	32.37
4	0.31	55.08	0.28	55.36	55.36	0.30	54.00	0.27	54.27	54.27
6	0.41	74.52	0.58	75.10	75.10	0.41	73.62	0.57	74.19	74.19
8	0.50	90.18	1.00	91.18	91.18	0.52	93.48	0.98	94.46	94.46

TABLE 9
IN VITRO RELEASE PROFILE OF FORMULATION F_9

Time	F9				
	concentration of Drug (mg)		cumulative loss	Cumulative drug release	
	5ml	900ml	Mg	mg	%
0	0.00	0.00	0.00	0.00	0.00
1	0.09	16.26	0.00	16.26	16.26
2	0.18	32.28	0.09	32.37	32.37
4	0.24	42.78	0.27	43.05	43.05
6	0.38	67.98	0.51	68.49	68.49
8	0.48	85.50	0.89	86.39	86.39
10	0.54	97.98	1.36	99.34	99.34



GRAPH NO. 3: *In vitro* drug release of Labetalol through Xanthan gum (F7, F8, F9)

3.5 *In vitro* drug release of Labetalol HCl through the Tamarind seed polysaccharide.

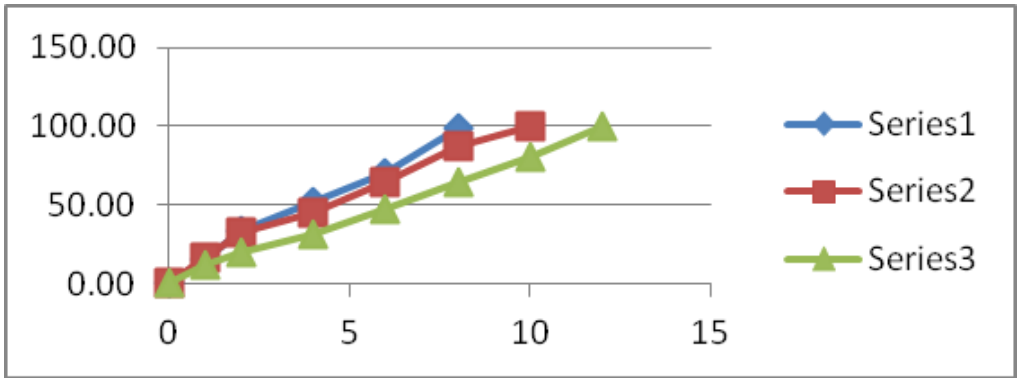
TABLE 10
***IN VITRO* RELEASE PROFILE OF FORMULATION F_{10} & F_{11}**

Time	F10					F11				
	Concentration of Drug (mg)		Cumulative loss	Cumulative drug release*		Concentration of drug (mg)		Cumulative loss	Cumulative drug release *	
	5ml	900ml	mg	mg	%	5ml	900ml	mg	mg	%
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.09	15.30	0.00	15.30	15.30	0.09	16.02	0.00	16.02	16.02
2	0.19	33.30	0.09	33.39	33.39	0.18	32.76	0.09	32.85	32.85
4	0.29	52.08	0.27	52.35	52.35	0.25	44.28	0.27	44.55	44.55
6	0.39	69.66	0.56	70.22	70.22	0.36	64.32	0.52	64.84	64.84
8	0.55	98.10	0.95	99.05	99.05	0.48	86.76	0.87	87.63	87.63
10	-	-	-	-	-	0.54	97.98	1.36	99.34	99.31

TABLE 11

***IN VITRO* RELEASE PROFILE OF FORMULATION F_{12}**

Time	F12				
	concentration of Drug (mg)		cumulative loss	Cumulative drug release	
	5ml	900ml	mg	mg	%
0	0.00	0.00	0.00	0.00	0.00
1	0.07	12.12	0.00	12.12	12.12
2	0.11	19.62	0.07	19.69	19.69
4	0.17	30.72	0.18	30.90	30.90
6	0.26	46.80	0.35	47.15	47.15
8	0.36	64.20	0.61	64.81	64.81
10	0.44	79.44	0.96	80.40	80.40
12	0.55	98.22	1.41	99.63	99.63



GRAPH NO. 4: in vitro drug release of Labetalol through Tamarind seed polysaccharide (F_{10}, F_{11}, F_{12})

IV. CONCLUSION

From the present study, The sustained release matrix tablet of Labetalol HCl using polymers such as HPMC K 15, Sodium CMC, Xanthan gum and Tamarind seed polysaccharide, prepared by wet granulation method were found to be good without chipping, capping and sticking. The drug content was uniform in all the formulations of tablets prepared. The low values of standard deviation indicate uniform distribution of drug within the matrices.IR and DSC studies indicated that the drug and polymers are in the pure form and compatible with each other. The drug-polymer ratio was found to influence the release of drug from the formulations. As the polymer concentration is increased, the drug release rates were found to be decreased. Formulation F3 and F12 with drug-polymer ratio 1:1 containing PVP K30 and MCC as binder and diluents respectively have shown promising results as per USP Test-I requirements. Sustained release matrix tablets of Labetalol hydrochloride can be prepared using HPMC K 15 and Tamarind seed polysaccharide achieve a desired drug release rates over a period of 12 hours, which can help to reduce the dose and frequency. Among the various formulations prepared, F3 and F12 appear suitable for further pharmacodynamic and pharmacokinetic evaluation in a suitable animal model.

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Synthesis and Biological Evaluation of Quinazolinone Derivatives as Antibacterial and Anti-Inflammatory Agents

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Abstract— *Some novel 6,8-diiodo-2-methyl-3-substituted-quinazolin-4(3H)-ones bearing sulfon- amide derivatives (4–11) were synthesized in good yields and evaluated for their possible antibacterial, anti-inflammatory activities and acute toxicity. The structures of the synthesized compounds were confirmed on the basis of their spectral data and elemental analysis. Their antibacterial activities were evaluated by the agar well diffusion method while their anti-inflammatory activities were evaluated by the carrageenan-induced hind paw edema test. All the tested compounds showed con- siderable antibacterial activities and high to moderate anti-inflammatory activities that last for 12 h compared to ibuprofen. All the tested compounds showed no toxic symptoms or mortality rates 24 h post-administration at tested anti-inflammatory doses. In addition, LD_{50} for all tested com- pounds was higher than that for ibuprofen implying their good safety margin. The obtained results showed that the most active compounds could be useful as a template for future design, modification and investigation to produce more active analogs.*

Keywords— Quinazolinone derivatives, Antibacterial Agents, Anti-Inflammatory Agents, Compound Sturcture.

I. INTRODUCTION

There is a strong relationship between bacterial infection and inflammation (Sy et al., 2011). Bacterial infection often produces pain and inflammation. Inflammation remains a com- mon with poorly controlled clinical problem which can be life threatening in extreme form of allergy, autoimmune diseases and rejection of transplanted organs (Gounon and Huerre, 1996). The treatment options which can be used for inflammatory diseases are unsatisfactory and complicated due to their lack of efficacy and adverse effect profile. It seemed worthwhile to look for candidates acting on more than one path- way involved in inflammatory conditions (Bot et al., 2011).

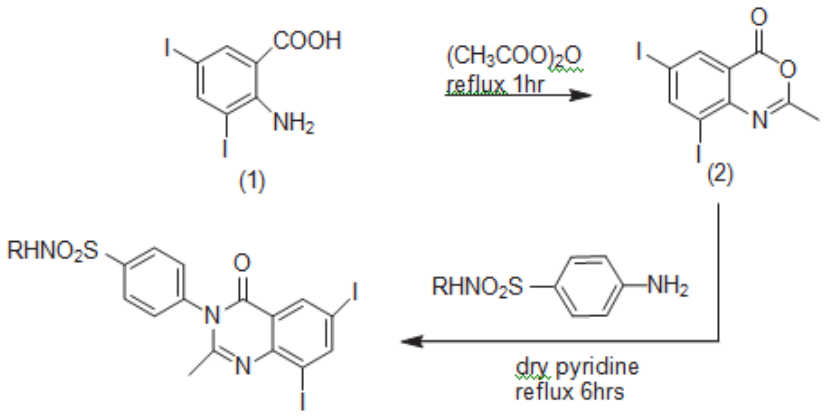
Quinazolin-4-one ring system has been consistently re- warded as a promising molecule because of its broad spectrum of pharmaceutical activities like antihistaminic (Lemura et al., 1989), anti inflammatory (Amin et al., 2010), antibacterial (Kini and Grover, 2006), antidiabetic (Ram et al., 2003), anti- cancer (Abbas et al., 2012), antifungal (Liu et al., 2006), anthelmintics (Connolly et al., 2005) and antiviral activities (Dinakaran et al., 2003). In addition to that, anti-inflammatory quinazolines possess remarkable anti-inflammatory activity through inhibition of tumor necrosis factor-alpha (TNF-a) and interleukin-6 (IL-6) (Rajan et al., 2010).

On the other hand, sulfonamide derivatives have been reported to possess significant antibacterial activities through competitive inhibition of dihydropteroate synthetase enzyme (DHPS) which is involved in folate synthesis (Skold, 2000). Moreover, some sulfonamides work as anti-inflammatory drugs like celecoxib which works as a COX-2 inhibitor (Gassani et al., 2010) and acetazolamide which works by diuretic mechanism (Jaiswal et al., 2004). On light of these findings, we planned to prepare the target com- pounds as hybrid molecules. These molecules contain the quinazolinone ring system and fused with sulfonamide derivatives to form a group of compounds resembling and collecting both features of nitrogen heterocyclic moiety and sulfonamide moiety. In addition, iodine atoms exist at 6th and 8th positions from quinazoline nucleus. Iodine was selected because it has received consider- able attention in organic synthesis due to its high tolerance to air and moisture, low-cost, nontoxic nature and ready availability. Presence of iodine increases the lipophilicity of the molecules, the surface of contact, the absorption and the distribution (Laznicek et al., 1985; Yanming et al., 2003).

1.1 Rationale of the study

A literature survey revealed that the presence of quinazoline moiety, which can undergo substitution at the heteroatom or the distal aromatic ring, is a necessary requirement for the anti- bacterial and anti-inflammatory activities such as compounds

[A] (Kini and Grover, 2006), [B] (Ali et al., 2010) and [C] (Pan- neerselvam et al., 2009). Moreover, quinazoline derivatives with the appropriate substituent mainly amine or substituted amine at 4th position and either halogen or electron rich substituent at 6th or 8th position are known to promote against bacteria and inflammation (Tiwari et al., 2006). In view of the previous rationale, it was thought worthwhile to study the effects of two pharmacophoric moieties like quinazolinone and sulfonamide in a single molecule on the antibacterial and anti-inflammatory activities. The target compounds have been designed to contain different substituents with different electronic environments. As shown in Scheme 1, these substituents joined to the fixed moiety (3) start with hydrogen from sulfanilamide in compound (4), acetamide from sulfacetamide in com- pound (5), benzamide from sulfabenzamide in compound (6), pyridine from sulfapyridine in compound (7), pyrimidine from sulfadiazine in compound (8), 5-methylisoxazole from sulfa-methoxazole in compound (9), 4,6-dimethylpyrimidin from sulfamethazine in compound (10) and 3,4-dimethyl-1,2-oxazole from sulfafurazole in compound (11). These varied substituents allow us to study the effect of hydrophilic and hydrophobic changes on the biological activity of the target compounds. Fig. 1 represents the similarities between the reported antibacterial and anti-inflammatory quinazolinones and our designed compounds.



3)

4) R = H
5) R = $COCH_3$
6) R = COC_6H_5
7) R = C_5H_4N
8) R = $C_4H_3N_2$
9) R = C_4H_4NO 10)R= $C_6H_7N_2$ 11)R= C_5H_6NO

SCHEME 1: Synthesis of the target compounds (4–11).

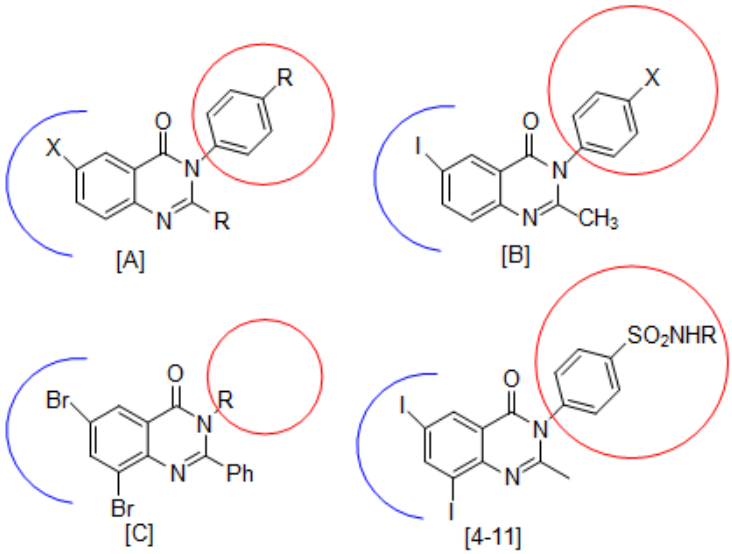


FIGURE 1 Similarities between reported compounds as antibacterial, anti-inflammatory and target compounds (4–11).

II. MATERIALS AND METHODS

2.1. Chemistry

The tested compounds were analyzed at the Analytical Center, College of Science, Cairo University, Egypt. All melting points were measured on a Griffin melting point apparatus (Griffin) and are uncorrected. The Infrared spectra were recorded as KBr disks on a Nicolet IR 200 (Thermo Fisher Scientific). The ^{1}HNMR and ^{13}CNMR spectra were run using TMS as an internal standard (Sigma–Aldrich) on Varian Mercury VXr-300 NMR (Varian). Mass spectra were obtained on a JEOL-SX-102 instrument using electron impact ionization. Elemental analyses (C, H, N) were performed on a Perkin–El- mer 240C analyzer (Perkin–Elmer). All compounds were with- in ±0.4% of the theoretical values. All chemicals used for synthesis were purchased from (Sigma–Aldrich).

2.2. Synthesis

The synthetic strategy to prepare the target compounds (4–11) is depicted in Scheme 1: it includes two simple reactions, first one is the acetylation/benzoylation followed by the ring clo- sure reaction for 2-amino-3,5-diiodobenzoic acid (1). Com- pound (1) when refluxed with acetic anhydride for one hour converted into benzoxazinone. This reaction afforded quanti- tative yield of 6,8-diiodo-2-methyl-4H-benzo[d][1,3]oxazin-4- one (2). Second reaction is a nucleophilic displacement reaction for the oxygen of benzoxazinone with the nitrogen of the amino group upon treating with sulfonamides. The second reaction was done by refluxing compound (2) with the appropriate sulfonamide in dry conditions for six hours to give sulfonamide derivatives of 6,8-diiodo-2-methyl-quinazolinone (4–11) in variable yields between 62% and 76%.

2.3. Pharmacology

2.3.1. Animals

The animals were procured from the Animal House Center, College of Pharmacy, King Abdulaziz University, Saudi Arabia, and were maintained in a colony cages at 25 ± 2 °C, relative humidity of 45–55%, under 12 h light and dark cycles; they were fed standard animal feed. All animals were acclimatized for a week before use. The protocol adopted for the experimentation of animals was approved by the Institutional Animal Ethics Committee (approval No: 409/432). All the experiments were carried out according to the respective inter- nationally valid guidelines.

2.3.2. Biological screening

All the newly synthesized compounds (4–11) were screened to evaluate their antibacterial and anti-inflammatory activities and acute toxicity. The antibacterial activity was performed by the agar well diffusion method while the anti-inflammatory activity was evaluated by the carrageen an induced rat Paw edema method using ibuprofen as a reference drug. The response of all the compounds to antibacterial activity is good however, some of the compounds showed promising anti- inflammatory activity. The other remaining compounds showed moderate anti-inflammatory activity. No toxic symptoms or mortality rates were observed 24 h post administration implying their good safety margin. The details of activity results are outlined below.

TABLE 1
ANTIBACTERIAL ACTIVITY OF TESTED COMPOUNDS (4–11)

Compound ID	Gram positive strains		Gram negative strains	
	S. aureus	*S. epidermis*	*P. aeruginosa*	*E. coli*
4	20	21	18	22
5	17	19	20	20
6	14	18	14	17
7	18	20	15	20
8	19	17	21	19
9	15	16	21	16
10	13	15	20	21
11	19	18	21	19
Streptomycin (standard)	21	23	24	29

Inhibitory zone diameters in mm; conc of standard 50 μg/ml, compounds 100 μg/ml.

2.3.3. Antibacterial activity

Antibacterial activity of all the test compounds was deter- mined by agar well diffusion method (Waynae, 1997) which is recommended by the National Committee for Clinical Lab- oratory Standards (NCCLS) against two kinds of Gram positive micro organisms Staphylococcus aureus (MTCC 96) and Staphylococcus epidermis (MTCC 435) and two kinds of Gram negative micro organisms Pseudomonas aeruginosa (MTCC 741), and Escherichia coli (MTCC443) at 100 lg/mL concentration using dimethylsulfoxide (DMSO) as a solvent.

The bacteria were sub-cultured on Mueller Hinton agar medium. Streptomycin was used as a standard antibacterial under similar conditions at a concentration of 50 lg/mL for comparison while solvent control was also maintained under similar conditions. The results of antibacterial screening are outlined in Table 1.

2.3.4. Acute toxicity

Toxicological studies of the synthesized compounds were per- formed using (LD_{50}) which is the dose that will kill 50% of the animal population within 24 h post treatment with the test substance. The toxicity test was performed using standard method in mice and rats (Ishii and Yoshikawa, 1993; Ecobi-chon, 1997; Upmanyu et al., 2011). When there is no information on a substance to be tested, for animal welfare reasons, it is recommended to use the starting dose of 300 mg/kg body weight. The animals were given the lowest dose of 300 mg/kg of the compounds at the first instance. Then the animals were observed for three days. They were treated orally with different doses of tested compounds (400, 600, 800, 1000, and 2000 mg/ kg). The animals were then observed for 24 h for any behavioral effects such as nervousness, excitement, dullness, in-coordination or even death. Results for LD_{50} were calculated and are reported in Table 2.

TABLE 2
ACUTE TOXICITY STUDIES IN MICE AND RATS

Compound No	LD_{50}(mg/kg)	
	Mice	Rats
4	1015	950
5	974	844
6	1300	1245
7	1136	1020
8	1035	985
9	1554	1470
10	1633	1580
11	1670	1513
Ibuprofen (standard)	750	650

LD_{50}: dose that kills 50% of animals within 24 h after drug administration.

2.3.5. Anti-inflammatory activity

Anti-inflammatory activity of all the test compounds was determined according to the reported method (Winter et al., 1962; Vogel, 2007) by carrageenan-induced hind paw edema test using ibuprofen as a standard drug. Briefly, Male or female rats are starved overnight. To insure uniform hydra- tion, the rats received 5 ml of water by stomach tube (con- trols), standard ibuprofen (25, 50 and 100 mg/kg), or test compounds (25, 50, 100 and 200 mg/kg) suspended in the same volume. One hour later, the rats were challenged by a subcutaneous injection of 0.1 ml of 1% solution of carrageenan (Sig- ma–Aldrich) into the plantar side of the left hind paw. The thickness of dorsoventral diameter of each rat was measured using a pair of dial thickness gauge calipers accurate to 0.001 cm^3 (Progressive Trading Corporation) 3, 6 and 12 h after induction of inflammation. The increase of paw volume after 3, 6 and 12 h was calculated as percentage compared with the volume measured immediately after injection of the irritant for each animal (0 h). Effectively treated animals show much less edema. The percentage of anti-inflammatory activity (% inhibition of inflammation) was calculated according to the following equation:

% inhibition ¼ ðLc — Lt=LcÞ× 100

Lt is the mean increase in paw thickness in rats treated with the tested compounds and Lc is the mean increase in paw thickness in control group.

Evaluation: The difference at the various time intervals gives some hints for the duration of the anti-inflammatory effect for each compound as reported in Table 3. Doses that exhibited 50% protection in addition to the relative potencies of the test compounds to ibuprofen were recorded for comparisons and are shown in Table 4.

TABLE 3
ANTI-INFLAMMATORY ACTIVITY AND DURATION OF TESTED COMPOUNDS AT 50 mg/kg USING CARRAGEEN AN INDUCED RAT PAW EDEMA METHOD.

Compound ID	Percent protection		
	3h	6h	12 h
4	39.14 ± 0.02*,**	56.26 ± 0.04*,**	51.41±0.24*,**
5	41.75 ± 0.65*,**	62.83 ± 0.61*,**	58.15±0.06*,**
6	27.2 ± 0.01*,**	38.15 ± 0.04*,**	36.41±0.25*,**
7	36.58 ± 0.47*,**	44.62 ± 0.09*,**	49.71±0.34*,**
8	27.92 ± 0.3*,**	41.14 ± 0.07*,**	39.61±0.67*,**
9	23.27 ± 0.71*,**	31.34 ± 0.06*,**	35.78±0.86*,**
10	20.56±.03*,**	27.47 ± 0.03*,**	34.58±0.43*,**
11	19.25 ± 0.71*,**	28.16 ± 0.02*,**	25.52 ± 0.6*,**
Ibuprofen (standard)	68.12 ± 0.61*	69.91 ± 0.74*	67.54 ± 0.07*

*,** ***Significant difference from negative control and ibuprofen (standard), respectively at P < 0.0001, using Tukey's test as post ANOVA test***

TABLE 4
ED_{50} AND RELATIVE POTENCY OF TESTED COMPOUNDS TO IBUPROFEN AT 6 h.

Compound ID	ED_{50} (mg/kg)	Relative potency
4	60	0.66
5	54	0.74
6	90	0.44
7	69	0.58
8	75	0.53
9	105	0.38
10	120	0.33
11	117	0.34
Ibuprofen (standard)	40	1.00

ED_{50} is the dose required to induce 50% inhibition of rat pawedema (50% anti-inflammatory effect). ED_{50} was calculated using instate program by plotting results at all doses levels; Ibuprofen was tested at a dose range from 25 to 100 mg/kg and tested compounds from 25 to 200 mg/kg.

III. RESULTS

Antibacterial assay of all the test compounds (4–11) showed good activities against both of Gram positive bacteria and Gram negative bacteria. These activities were ranged from 61.91% up to 95.23% from the activity of the standard. The activity data generated are tabulated in Table 1. The anti- inflammatory screening showed that compounds (6, 7, 8, 9, 10 and 11) were considered to have moderate anti-inflammatory activity however, compounds (4 and 5) showed consider- able inhibition as shown in Tables 3 and 4. No toxic symptoms or mortality rates were observed 24 h post-administration at all suggested therapeutic doses however, the LD_{50} for most of tested compounds is much higher than that reported for ibuprofen. Concerning other actions, compounds 7, 8 and 11 induced urination while compounds 4, 5 and 6 induced sedation, calmness, muscle relaxation and decreased respiration.

IV. DISCUSSION

Inspection of the chemical structure of the target compounds suggested that target compounds could be divided into two subunits: the quinazolinone part and the sulfonamide part (Fig. 1). The two parts have been reported to have significant broad spectrum of antibacterial activities which might contribute to the good results obtained from testing them as antibacterial agents. Moreover, substitution of the distal aromatic ring from quinazolinone moiety with iodine at 6th and 8th positions might also helped in obtaining such good results.

For the anti-inflammatory activity, compounds with ali- phatic side chain (4) and (5) were more active than that with aromatic one. Compound (5), the most active compound among all the test compounds, contains aliphatic side chain. The relative potency of this compound was 74% of the reference's potency, as shown in Table 4. Pyridine containing com- pound (7) was more active than those with pyrimidine or oxazole instead. Within the pyrimidine and oxazole derivatives, dimethylated derivatives (10) and (11) were less active than monomethylated one (9) and methyl free one (8). The results of acute toxicity test which have been done to all test compounds indicated to their good safety margin. Although the title compounds exhibited potent antibacterial and anti- inflammatory actions, moderate anti-inflammatory activity was found. Hence, necessary structural modifications are planned in the future study to increase the anti-inflammatory activity. In general, the present study showed that compound

(5) was the most active compound with combined ability to inhibit bacterial infection and inflammation. This compound could therefore serve as a lead molecule for further modification to obtain clinically useful antibacterial and anti-inflammatory agents.

V. CONCLUSION

We have synthesized and tested some novel 6,8-diiodo-2- methyl-3-substituted-quinazolin-4(3H)-ones derivatives for their antibacterial and anti-inflammatory activities. All com- pounds induced significant antibacterial activity. Two com- pounds showed promising anti-inflammatory activity while the other five compounds showed moderate anti-inflammatory activity. All Compounds were tested for acute toxicity and showed good safety margin.

STATISTICAL ANALYSIS

Data obtained were expressed as means. Statistical difference between the treated and the control groups was evaluated by One Way Analysis of Varian (ANOVA) followed by the Tu-key's test as a post ANOVA multiple comparison test (Sigma Stat version 3; SPSS Inc.) to determine the statistical significance. A P value <0.05 was considered statistically significant.

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