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Solvent evaporation method of preparation of nanoparticle and in-vitro drug release study of Methylphenidate Hydrochloride

Anju Singh
Department of Biotechnology, Faculty of Engineering and Technology, Rama University, G.T. Road, Kanpur - 209217, India

Ajay Kumar
Department of Biotechnology, Faculty of Engineering and Technology, Rama University, G.T. Road, Kanpur - 209217, India
*Corresponding author email: ajaymtech@gmail.com

***Abstract*---**The purpose of this work was to develop Methylphenidate Hydrochloride nanoparticles, which would reduce dose frequency. Since they are non-toxic and may be utilised to construct long-acting dosage forms, polymeric nanoparticles have gained a lot of attention in recent years. Congestive heart failure, edoema, and renal failure are among the disorders for which the diuretic melphenidate hydrochloride is prescribed. Because of their exceptional stability, polymeric nanoparticles are an excellent substrate for long-term release. In other words, the half-life of methylphenidate hydrochloride (2.4 hours for children, and 2.1 hours for adults) is so short that it is only effective for a very short duration. Nanoparticles are the primary subject of this investigation. Using Eudragit RL 100 as a release retardant is possible. Therapeutic effectiveness is increased by maintaining a consistent plasma concentration of Methylphenidate Hydrochloride from nanoparticles. The new methylphenidate hydrochloride sustained release formulation proved to be a success in reducing the issues associated with the previous one.

***Keywords*---**nanoparticles, methylphenidate hydrochloride, in vitro drug release study.

Introduction

Our everyday lives have grown more dependent on nanotechnology, from electrical gadgets to medicines to cosmetics and the food and beverage sectors. Because they cannot reach specific cell compartments or are not prepared for the situation in which they will be used, traditional drugs are overprescribed and ineffective [1].

Prior to their use in drug delivery, polymeric nanoparticles were investigated for their capacity to boost bioavailability, regulate drug release from a single dose, and keep pharmaceuticals fresh until they reached their target location [2]. In order to create polymeric nanoparticles, there are several methods. For example, particle diameter and polydispersity in the application, as well as how the drug is integrated into nanotransporters, are determined by the synthesis processes [3].

Polymer, whether synthetic or natural, should be considered in addition to the synthesis process. For their biocompatibility, biodegradability, and surface modification abilities, natural polymers are a standout in the sector. Because of their wide range of possible uses as biopolymers, collagen, albumin, and gelatin have all received substantial research attention. Various features of synthetic polymers may be tailored to meet particular needs, such as improving the bioavailability or minimising the toxicity of a compound's compound-specific specificity [4]. Interactions between these polymers and biological systems with various compositions and surface features are driving the development of new and better technologies. Polymers classified as "smart" may react to changes in pH and temperature, as well as external stimuli, to enable active vectoring. Hydrophilic polymers such as vinyl esters, double esters, and hydrazones, are widely utilised to react to inflamed or malignant tissues or lysosomal conditions in order to release the active component of the substance [5]. The creation of nanoparticles has considerably benefitted the pharmaceutical industry. Improved delivery systems, diagnostic and treatment procedures, and the development of novel diagnostic and therapeutic approaches have made it easier to understand biological pathways [6]. Consequently, this study focused on polymeric nanoparticle manufacturing techniques and mechanisms of controlled release for biological applications.

Methodology

Method of preparation of methylphenidate hydrochloride nanoparticles Solvent Evaporation Method

All batches of nanoparticles were produced through solvent evaporation. ethanol, 50 mg sodium dodecyl sulphate diluted in water, and the quantity of medication and polymer dissolved in this mixture are the ingredients for the first part (II portion). As a final step, sodium dodecyl sulphate solution was used to mix the medication and polymer combination through injection. The mixture was sonicated for size reduction at a power output of 90W after being homogenised for one minute using a vortex mixture. After solvent drying, the dried nanoparticles were collected using a flash evaporator [7].

Table 1
Methylphenidate hydrochloride nanoparticle production method

S. no.	Formulation code	Drug (Methylphenidate hydrochloride) in mg	Polymer Eudragit RL 100
1	F1	20	10
2	F2	20	20
3	F3	20	30

4	F4	20	40
5	F5	20	50
6	F6	20	60
7	F7	20	70
8	F8	20	80
9	F9	20	90
10	F10	20	100

Evaluation of nanoparticles
Drug entrapment study

A UV spectrophotometric method was used to determine the free drug content in the supernatant after ultra centrifugation at 15,000 rpm for 20 minutes at 0°C [8].

In-vitro drug release studies
Scanning Electron Microscopy (SEM)

The enhanced formulation's morphology was examined using SEM (SEM). SEM analysis of the material was carried out by attaching small sample wads directly to scotsch double adhesive tape. Using a 15Kv hitachi scanning electron microscope, we were able to take a quick picture [9].

Surface charge (zeta potential) determination

It is critical to understand how a colloidal or dispersed system behaves in terms of its zeta potential in order to create an environment that is as stable as possible. The zeta potential of the generated nanoparticle suspension was analysed using a zeta potential analyzer (Malvern Zeta Seizer). The stability of a medicine is dependent on the presence of electrical charges on the particle's surface. Eudragit RL 100 was tested on the nanoparticle's surface to evaluate how it impacted its surface characteristics [9].

pH and physical appearance

The formulation's pH was measured using a pH metre. Stability and formulation are dependent on it. Examine the colour and any dissolved foreign particles of the formulation [9].

Stability studies of nanoparticles

An accelerated environment of 45°C/70 percent relative humidity is used to assess nanoparticle stability, as is a refrigerator at 4°C as well as the natural ambient temperature. The formulations were kept at both temperatures for three months prior to the studies, and a sufficient number of sample was collected on a regular basis [9].

Results and Discussion

Preparation of methylphenidate hydrochloride nanoparticles

In this study, Methylphenidate Hydrochloride Nanoparticles were synthesised using the Eudragit RL 100 solvent evaporation process. The medication (Methylphenidate hydrochloride) and polymer were both dissolved in ethanol (Eudragit). The solution containing 0.50mg sodium dodecyl sulphate dissolved in water was diluted with 5ml of the other solution and used. The mixture was first homogenised in a vortex for a minute before being sonicated. This mixture was then evaporated for 20 minutes in a flash rotator evaporator. Many different types of formulations were made. All aspects of nanoparticle structure, particle size, drug release profile and formulation stability at various temperatures were examined in this research.

In vitro drug release profile of nanoparticles

Membrane diffusion was used to study Methylphenidate hydrochloride nanoparticle drug release for 24 hours in vitro. Nanoparticles containing Methylphenidate hydrochloride and Eudragit RL 100 polymer were investigated in vitro for drug release. The in vitro release of medicine by Formulation F1 (Methylphenidate hydrochloride 20mg, Eudragit RL100 10mg). In only six hours, 99.45% of the drug had been delivered into the patient's bloodstream. Within six hours after its creation, the drug is made available to patients. As a result, the percentage of drug release was 98.46% and 97.45% in 8 hours for formulations F2, F3 with varying polymer concentrations (Methylphenidate hydrochloride 20 mg with Eudragit RL 100 20 mg, 30 mg). Those formulations that shown a rapid (8-hour) release (8hours). Low polymer content is a factor. For example, the drug release percentage was 99.48% after just 13 hours, 99.49% after 15 hours, 97.47% after 19 hours, and a whopping 99.49% after 20 hours in formulations with greater polymer concentrations and lower repulsive forces. With increasing polymer concentration, the percentage of drug release in 24 hours increased from 93.45 percent to 99.49 percent. Formulation F10 (Methylphenidate hydrochloride 20 with Eudragit RL 100 200mg) has a 24 hour drug release percentage of 56.29 percent. Medication release is increased by 56.29 percent when polymer concentration is raised. For further analysis, formulation F9 was chosen as the best one of the aforementioned formulations (F1-F10) because of its high percentage of drug release (99.49 percent) in comparison to the other formulations (F1 to F10).

Table 2
In vitro drug release for F9

Time (h)	Amount of drug release (mg)	% of drug release	Cumulative % drug release
1	0.3	0.3	3
2	0.8	0.80	8.03
3	1.3	1.30	13.05
4	1.7	1.70	17.08
5	2.2	2.21	22.10

6	2.8	2.81	28.12
7	3.3	3.31	33.15
8	3.9	3.91	39.18
9	4.4	4.42	44.21
10	4.7	4.72	47.23
11	5.1	5.12	51.25
12	5.5	5.52	55.27
13	5.9	5.92	59.29
14	6.2	6.23	62.31
15	6.6	6.63	66.32
16	7.0	7.03	70.34
17	7.4	7.43	74.36
18	7.9	7.93	79.38
19	8.2	8.24	82.41
20	8.6	8.64	86.42
21	8.9	8.94	89.44
22	9.2	9.24	92.46
23	9.5	9.54	95.47
24	9.9	9.94	99.49

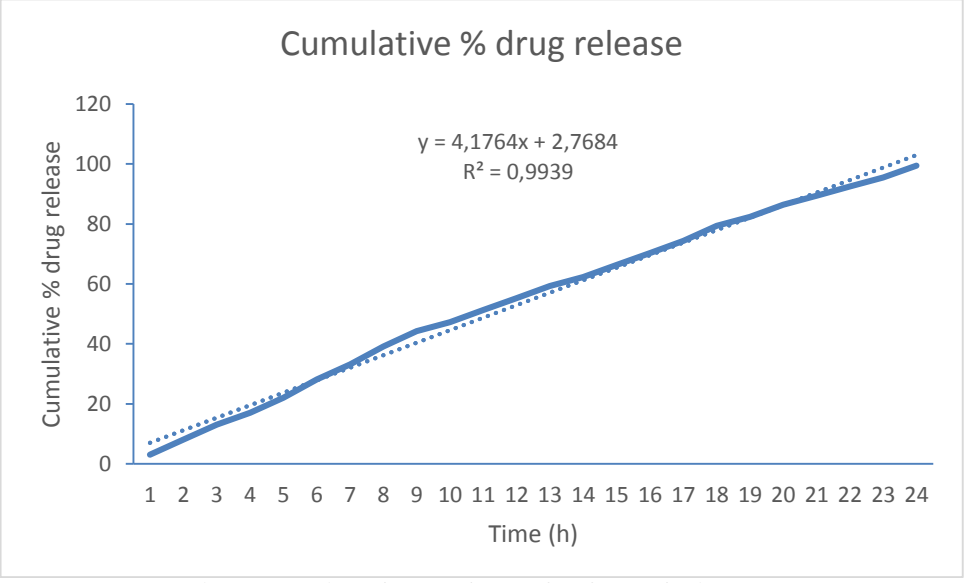

Fig. 1. *In-vitro* drug release for formulation F9

Scanning Electron Microscopy

Using SEM, the surface characteristics of the best formulation's (F9) particle size were analysed. The polymer coating on the drug particle may be seen via SEM imaging. Scanning Electron Microscopy reveals a granule-like appearance of nanoparticles covering the medicine, indicating an even and thin coating (SEM).

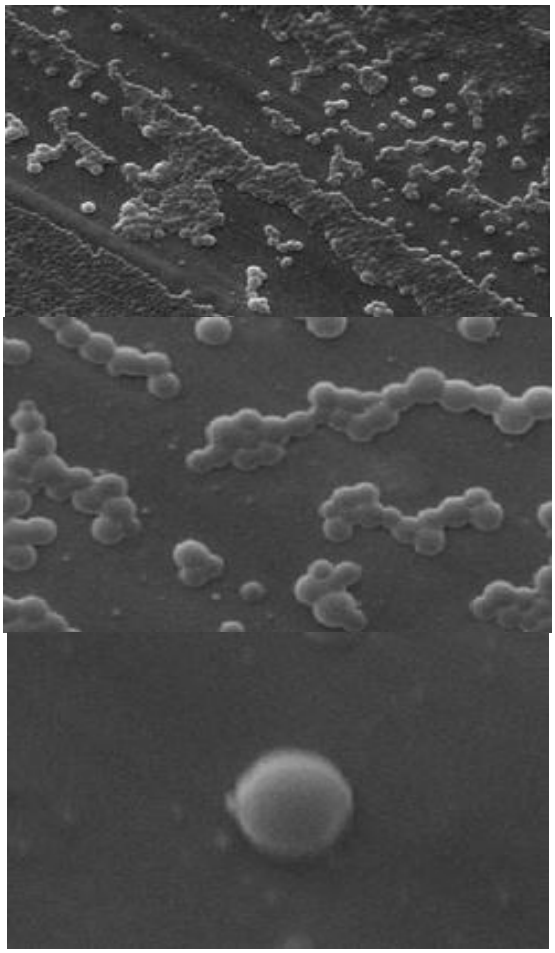

Fig. 2. SEM FOR F9

Surface charge (Zeta potential)

When discussing the surface charge of a nanoparticle, potential is typically used. A particle's ability to conduct electricity depends on its composition and how it is dispersed in its surroundings. Nanoparticle formulations are rapidly recognised and identified by phagocytes when delivered intravenously. The opsonin adsorption of blood components is affected by the nanoparticle's particle size and hydrophobicity surface. These opsonins have the last say on the fate of the nanoparticles. These opsonins are considered to be opsonized when they are adhered to the surface. Non-modified nanoparticles were promptly opsonized and are easily eliminated from human systems. In order to maximise the efficacy of drug targeting by nanoparticles, it is necessary to lower the opsonization and lengthen the nanoparticle circulation period in vivo. When Eudragit RL 100 is used, the formulation has the lowest conductivity (Ms/CM), 59.0 mV zeta potential, and the highest zeta deviation (Mv) of 5.29. Polymers are more suitable for the production of nanoparticles due to their flat surface, which deters opsonization.

Stability studies of methylphenidate hydrochloride nanoparticles

The enhanced nanoparticle formulation F9's stability was examined for a period of three months. During the trial, temperatures varied from 4°C to 45°C/70% RH. Every month for a year, nanoparticle compositions were tested for entrapment efficiency. The nanoparticles formulation was more stable in the refrigerator (4°C) than at ambient temperature and (45°C/70 percent RH).

Table 3
Methylphenidate hydrochloride nanoparticle stability studies

S. no.	Storage Condition	Test parameters	1st month	2nd month	3rd month
1	4 °C	pH	7.4	7.4	7.4
		colour	Clear & colourless	Clear & colourless	Clear & colourless
		Cumulative % drug release	99.49	98.27	97.90
2	Room Temperature	pH	7.4	7.4	7.3
		colour	Clear & colourless	Clear & colourless	Clear & colourless
		Cumulative % drug release	99.49	94.38	92.87
3	Acceleration condition at 45°C/70°% RH	pH	7.4	7.3	7.3
		colour	Clear & colourless	Clear & colourless	Clear & colourless
		Cumulative % drug release	96.12	92.23	90.26

Table 4
Stability analysis at 4°C of the improved formulation F9 *in vitro* release

Time (h)	Cumulative % drug release		
	1st month	2nd month	3rd month
1	3	3	2.8
2	8.03	8.03	7.00
3	13.05	13.02	12.98
4	17.08	17.04	16.00
5	22.10	22.06	22.02
6	28.12	28.06	28.02
7	33.15	33.10	33.00
8	39.18	39.04	38.98
9	44.21	44.08	43.94
10	47.23	46.98	46.90
11	51.25	50.92	50.77
12	55.27	54.93	54.65
13	59.29	58.56	57.24
14	62.31	61.90	61.16

15	66.32	65.52	64.98
16	70.34	70.04	69.88
17	74.36	73.16	73.04
18	79.38	79.05	78.97
19	82.41	81.70	81.71
20	86.42	85.68	85.24
21	89.44	88.23	88.03
22	92.46	92.19	92.17
23	95.47	95.07	94.59
24	99.49	98.27	97.90

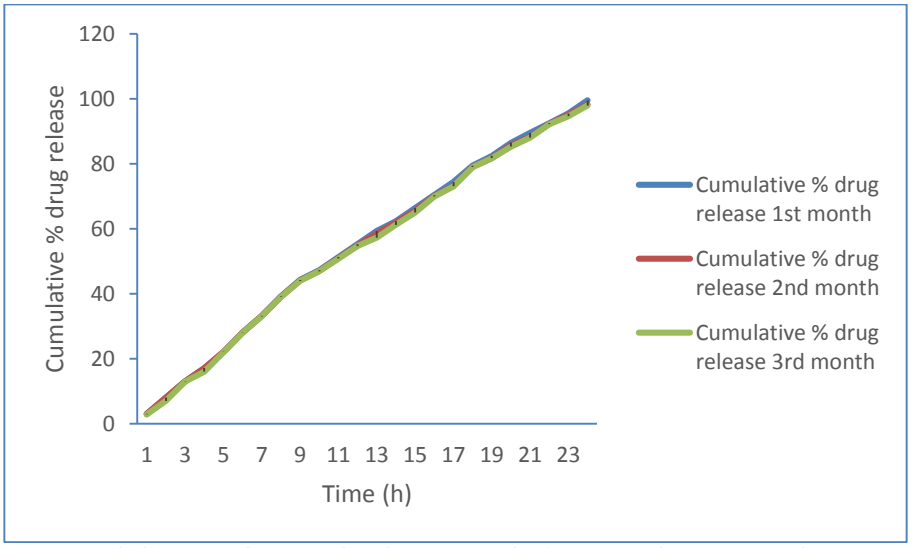

Fig. 3. Stability Study Results for Formulation F9 After 3 Months at 4 °C

Table 5
At room temperature, in vitro data for an improved formulation of F9 was collected

Time (h)	Cumulative % drug release		
	1st month	2nd month	3rd month
1	3	2.8	2.7
2	8.03	7.90	6.14
3	13.05	10.94	9.23
4	17.08	15.00	13.12
5	22.10	20.14	17.16
6	28.12	24.18	22.50
7	33.15	29.21	26.54
8	39.18	35.30	33.60
9	44.21	41.34	38.68
10	47.23	45.44	42.74
11	51.25	49.52	44.80
12	55.27	52.58	48.89

13	59.29	55.65	51.97
14	62.31	58.71	55.04
15	66.32	63.77	60.10
16	70.34	67.57	64.18
17	74.36	72.64	69.24
18	79.38	76.69	73.34
19	82.41	79.78	77.40
20	86.42	81.87	79.50
21	89.44	85.98	82.58
22	92.46	88.08	86.68
23	95.47	91.19	89.74
24	99.49	94.38	92.87

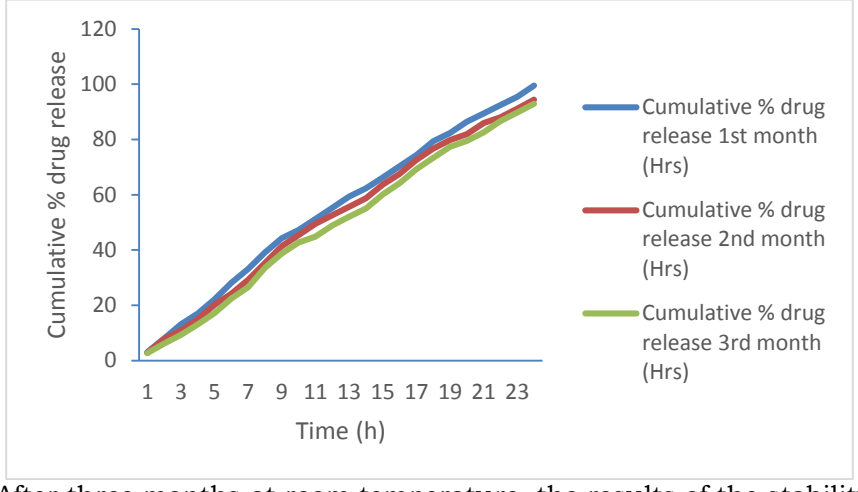

Fig. 4. After three months at room temperature, the results of the stability study were released for Formulation F9

Table 6
At 45 °C and 75% RH, we collected in vitro data for an improved formulation F9 study

Time (h)	Cumulative % drug release		
	1st month	2nd month	3rd month
1	3	2.8	2.4
2	8.54	7.46	6.36
3	12.08	11.50	9.41
4	16.16	14.58	12.47
5	20.22	17.64	15.53
6	24.30	20.70	17.60
7	27.38	24.80	20.74
8	31.46	28.88	25.80
9	34.52	30.98	28.85
10	37.58	32.10	30.91
11	41.68	35.18	33.98

12	46.74	39.27	36.23
13	50.23	44.17	37.89
14	55.30	47.08	41.63
15	60.87	60.18	55.33
16	64.23	64.28	59.00
17	69.26	68.08	62.05
18	73.61	72.14	66.15
19	77.31	75.34	70.38
20	81.60	80.23	75.19
21	85.86	83.15	78.18
22	88.23	87.30	82.38
23	92.64	90.28	86.23
24	96.12	92.23	90.26

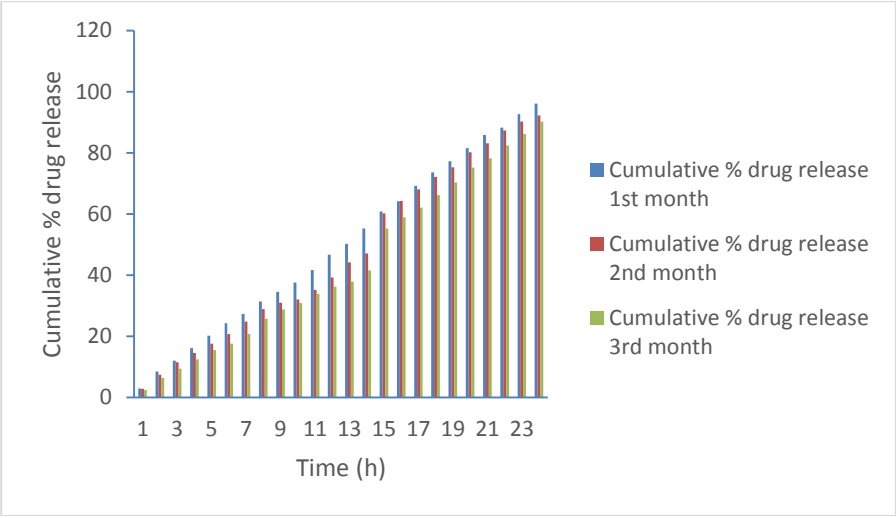

Fig. 5. A 45°/75 percent RH STUDY TO DEVELOP THE OPTIMIZED F9 formulation

Stability Discussion

Three months of stability testing were conducted in a variety of settings. A stable formulation was observed throughout the study period.

Conclusion

Eudragit RL100, a biodegradable polymer, is used to disseminate methylphenidate hydrochloride nanoparticles in the present study. Each batch of nanoparticles was made using the solvent evaporation method (F1-F10). After 24 hours of incubation, in vitro drug release was 98.16, with an entrapment efficiency of 940.04 for the enhanced formulation. This is the next step after the zero order. As measured by scanning electron microscopy, a 200-nm average particle size is ideal. The formulation passed the stability test with flying colours. The ideal formulation was put to the test in order to figure out its zeta potential. The formulation F9 demonstrates that the particles are separated and particularly

repellent due to its largest variation of -59mV. An anti-opsonization effect was found in membrane filtration to be more helpful. Stability testing was place over the course of three months in a number of locations. The testing period yielded a stable formulation. F9's commercial viability will be assessed if bioequivalence tests are conducted in the future. The major objective of the project was to optimise the formulation parameters.

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