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DEVELOPMENT AND EVALUATION OF PARACETAMOL SUPPOSITORIES

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ABSTRACT

Suppositories are supposed to be efficient and effective dosage form specially to dispense analgesics and antipyretics. Paracetamol is widely used as antipyretic and analgesic. When used in the form of suppositories it produces rapid effects due to its quick absorption through the rectal route. During the present study, Paracetamol suppositories are formulated by using different ratios of Polyethylene Glycol 1000 and polyethylene Glycol 4000. The in vitro drug release rate studies were carried out by using B.P dissolution apparatus. The average weight variation of different ratios of Paracetamol suppositories are; 2.5168 gm for the ratio of (3.35-0.65), 2.5193 gm for the ratio of (3.00-1.00), 2.5308 gm for the ratio of (2.00-2.00), 2.5378 gm for the ratio of (1:00-3.00), 1.83 gm for marketed suppository (Napa). The average hardness of different ratios of Paracetamol suppositories are; 6.67 kg for the ratio of (3.35-0.65), 7.21 kg for the ratio of (3.00-1.00), 8.44 kg for the ratio of (2.00-2.00), 8.27 kg for the ratio of (1:00-3.00), 6.93 kg for marketed suppository (Napa). The melting time of different ratios of Paracetamol suppositories are; 27 minutes at 37°C for the ratio of (3.35-0.65), 37 minutes at 37°C for the ratio of (3.00-1.00), 1 hour at 37°C for the ratio of (2.00-2.00), 1 hour and 15 minutes at 37°C for the ratio of (1:00-3.00), 28 minutes at 37°C for marketed suppository (Napa). The % release of different ratios of Paracetamol suppositories are; 99.05% in 30 minutes for the ratio of (3.35-0.65), 98.53% in 30 minutes for the ratio of (3.00-1.00), 97.79% in 30 minutes for the ratio of (2.00-2.00), 96.33% in 30 minutes for the ratio of (1:00-3.00), 99.26% in 30 minutes for the ratio of marketed suppository (Napa) respectively. It is expected that present work will be helpful for the selection of appropriate ratio of suppository bases to get the maximum % release of drug.

KEYWORDS: Paracetamol, Uniformity of weight, Hardness, Melting time, Dissolution (In vitro release study).

INTRODUCTION

➢ **Paracetamol (Acetaminophen)**

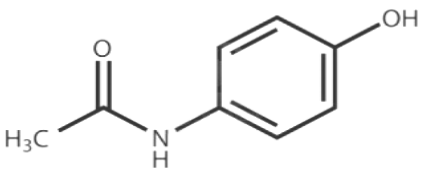
Acetaminophen inhibits prostaglandin in the CNS.This explains its antipyretic and analgesic properties. Acetaminophen has less effect on cyclooxygenase in peripheral tissues, which accounts for its weak anti-inflammatory activity. Acetaminophen does not affect platelet function increase blood-clotting time. Acetaminophen is not considered to be an NSAID.

Pharmaceutical Assessment

Drug Substance

Chemical Name: N-(4-hydroxyphenyl) acetamide

Structure



Molecular formula: C8H9NO2

Molecular weight: 151.2 g/mol

Physical form

Physical form: A white or almost white, crstalline powder.

Solubilty: Sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride.

Adverse effects: With normal therapeutic doses, acetaminophen is virtually free of any significant adverse effects. Skin rash and minor allergic reactions occur infrequently. There may be minor alterations in the leukocyte count, but these are generally transient. Renal tubular necrosis a rare complication of prolonged, large-dose therapy. With large episodes of acetaminophen , the available glutathione in the liver becomes depleted, and N-acetylbenzoiminoquinone reacts with the sulfhydryl groups of hepatic proteins, forming covalent bonds. Hepatic necrosis, very serious and potentially life-threatening conditions can result. Patients with hepatic disease, viral hepatitis, or history of alcoholism are at higher risk of acetaminophen-induced hepatotoxicity. Renal tubular necrosis may also occur. This agent

should be avoided in patients with the severe hepatic impairment. Periodic monitoring of liver enzymes test is recommended for those on high dose acetaminophen.

Types of Suppositories

a) Rectal suppositories
b) Vaginal suppositories
c) Urethral suppositories
d) Nasal Suppositories
e) Ear cones

➢ **Factors affecting the Rectal Absorption**

• **Physiologic Factors**

Among the physiologic factors affecting drug absorption from the rectum are the colonic contents, circulation route, and the pH and lack of buffering capacity of the rectal fluids.

a. Colonic Content
b. Circulation Route
c. pH and lack of buffering capacity of the rectum.

• **Physicochemical Factors of the drug**

a. Lipid-water solubility
b. Particle size

➢ **Types of Suppository Bases**

Four main types of bases are available:

(1) Oily bases

a. Cocoa Butter (Theobroma Oil)
b. Emulsified theobroma oil

(2) Hydrophilic bases

a. Glycerinated Gelatin
b. The Polyethylene Glycols (Macrogols)
c. Soap Glycerin.

(3) Water dispersible bases

(4) Emulsifying bases.

a. Massa Estrinum (Adeps Solidus)

b. Massupol

c. Witepsol

d. Wecobee Bases

➢ **Methods of Preparation**

- Hand molding
- Compression Molding
- Fusion Molding

MATERIALS AND METHODS

Paracetamol was gifted from Medisure Pharma Karachi Pakistan as a sample. (Anhui Suntran Chemical Co., Ltd. CHINA).

➢ **Polyethylene glycol 1000 :**BDH laboratory Supplies analytical grade , poole, BH 15 LTD ENGLAND

➢ **Poly Ethylene glycol 4000:** BDH laboratory Supplies analytical grade , poole, BH 15 LTD ENGLAND

➢ **Hydrogen Orthophosphate:** sigma-Aldrich Laboratories analytical grade,Chemikallen GmbH D-30926 sselz

➢ **Citric Acid:** Anhui Suntran Chemical Co., Ltd.

➢ **Natural Oil:** Kay Chemist Pvt Ltd .

Equipments

➢ **Balance:** mettlerToledo B201-S, No. 1120161890, Switzerland &Sarotorious CP224S, no.14411659, Germany.

➢ Moulds (Dyes)

➢ **Refrigerator:** Zoppas (Medium)

➢ **Electrical Burner:** Gallen hamp Magnetic stirrer hotplate 400

➢ **Dissolution Apparatus:** Erweka DT 700 & ZT-2 Husenstamm, Germany.

➢ **Hardness tester:** OSK Fujiwara Seiki Co. Ltd., Tokyo, Japan**.**

➢ **PH Meter**: MP220 Mettler Toledo, No. 200219M, GmbH, Switzerland

➢ **Spectrophotometer:** UV-1800, Double beam spectrophotometer, No. A114545 ShimadzuCorporations, Tokyo. Japa**n**

- Spatula, Waterbath, Beaker, Thermosterrir 95, Thermometer, Stand, Flask, Stirrer.

Calculation for formulation 0f 10 suppositories paracetamol 650 mg

Calculation of API Paracetamol for 10 suppositories

650mg X 10 = 6500 /1000 = 6.5 gm

Ratio 3.35-0.65 (84% - 16%)

2.5g weight of one suppository in cavity (Total suppositories 10)

2.5 X 10 = 25 gm

PEG 1000 = 84 / 100 X 25 = 21 gm

PEG 4000 = 16 / 100 X 25 = 4g.

Ratio 3.00-1.00 (75% - 25 %)

2.5g weight of one suppository in cavity (Total suppositories 10)

2.5 X 10 = 25 gm

PEG 1000 = 75 / 100 X 25 = 18.75 gm

PEG 4000 = 25 / 100 X 25 = 6.25 gm

Ratio 2.00-2.00 (50% - 50%)

2.5g weight of one suppository in cavity (Total suppositories 10)

2.5 X 10 = 25 gm

PEG 1000 = 50 / 100 X 25 = 12.5 gm

PEG 4000 = 50 / 100 X 25 = 12.5 gm

Ratio 1.00-3.00 (25% - 75%)

2.5g weight of one suppository in cavity (Total suppositories 10)

2.5 X 10 = 25 gm

PEG 1000 = 25 / 100 X 25 = 6.25 gm

PEG 4000 = 75 / 100 X 25 = 18.75 gm

PREPARATION OF PARA CETAMOL SUPPOSITORIES (650 mg)

(3.35-0.65) Ratio	**(3.00-1.00) Ratio**
Paracetamol= 6.5 gm	Paracetamol= 6.5 gm
PEG 1000= 21 gm	PEG 1000= 18.75 gm
PEG 4000= 4 gm	PEG 4000= 6.25 gm

(2:00-2:00) Ratio	(1.00-3.00) Ratio
Paracetamol= 6.5 gm	Paracetamol= 6.5 gm
PEG 1000= 12.5 gm	PEG 1000= 6.25 gm
PEG 4000= 12.5 gm	PEG 4000= 18.75 gm

PREPARATION OF PARA CETAMOL SUPPOSITORIES (650 mg)

Procedure

1) Melt the calculated amount of PEG 1000 and PEG 4000 in a graduated beaker over water bath after melting keep down from water bath.

2) Add required quantity of paracetamol and mix thoroughly

3) Pour the melted mass into the cavities of the mould which is already cool by keeping them in deep freezer for dry and mineral oil layer is used with the help of swab on the mould cavities for lubrication.Keep the melted mass cavities of the mould in the fridge at 2-8°C for 45 minutes to 1 hour.

4) Allow the mass to solidify, when the mass is solidified; turn off excess mass with knife or spatula.

5) Open the moulds to remove the suppositories.

6) If any lubricant is present wipe it off with filter paper or clean cloth.

7) Wrap the suppositories in butter paper and keep in fridge at 2-

Pharmacopoeial Control Test

Uniformity of Weight Test: All the suppositories should be uniformed in weight. The weight variation may result if some cavities are under filled and others are overfilled.

To perform this test 20 suppositories are weighed and average weight is calculated. The each suppository is weighed individually and weight noted. No suppository should deviate from the average weight by more the 5%.

Results are mentioned Table #1.

Hardness Test

Mechanical strength which determines of the mechanical force necessary to break a suppository and indicates brittle or elastic nature of the suppository.Erweka Suppository hard tester (TYPE SBT, Germany) was used to determine the hardness or breaking point of a suppository.

The apparatus measures the force under which suppository collapse. The hardness is calculated for 20 suppositories: Results are mentioned in Table # 2.

Melting Time

This test is also known as macro melting range test. During this test the time taken for entire suppository to melt is measured when immersed in at constant temperature (37°C) water bath. Results are mentioned in Table # 3.

Dissolution Test (In Vitro Release Study)

Dissolution test for the various paracetamol suppositories was carried out by using dissolution apparatus B.P. The suppository was placed in a beaker with a stirrer at a height 2mm from the bottom of the beaker. The stirrer rotated 100rpm and the system was maintained at constant temperature of 37°C ± 1°C. 5ml sample was taken at different time intervals 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 minutes and replaced with 5ml of fresh medium maintained at same temperature. Samples were filtered suitably diluted and assayed spectrophotometrically at 243nm.

Absorbance of reference Standard value is 0.954 at 243nm.

Results are mentioned in Table# 4 and in Figure#1

Sample Preparing Procedure for Spectroscopy

1) Take 5ml sample from dissolution apparatus and filter it with filter paper in test tube.

2) Take 5ml filtered sample in 25ml volumetric flask and make the volume with Phosphate buffer 7.2.

3) Take 5ml sample from above solution in 25ml volumetric flask and make the volume with Phosphate buffer 7.2.

4) Take 2 to 3 ml sample from above solution for spectroscopy.

Preparation of phosphate buffer ph 7.2 (B.P 2005): Mix 87.0 ml of a 7.15% w/v solution of disodium hydrogen orthophosphate with 13.0 ml of a 2.1% w/v solution of citric acid.

RESULT

Table. 1: Weight Variation of paracetamol Suppositories in gms.

S#	3.35-0.65	3.00-1.00	2.00-2.00	1.00-3.00	Napa 250mg
1	2.5159	2.5288	2.5779	2.5467	1.83
2	2.5362	2.5058	2.5469	2.5408	1.61
3	2.5287	2.5369	2.5082	2.5387	1.96
4	2.5053	2.5156	2.5726	2.5332	2.00
5	2.5121	2.5059	2.4840	2.5056	1.69
6	2.5102	2.5127	2.5203	2.5605	1.91
7	2.5245	2.5249	2.5044	2.5108	1.73
8	2.5050	2.5321	2.5395	2.5401	1.89
9	2.5212	2.5258	2.5264	2.5205	2.01
10	2.5133	2.5059	2.5290	2.5409	1.85
11	2.5351	2.5153	2.5389	2.5601	1.73
12	2.5150	2.5259	2.5513	2.5581	1.88
13	2.5258	2.5056	2.5069	2.5319	1.62
14	2.5059	2.5105	2.5281	2.5211	1.75
15	2.5319	2.5259	2.5111	2.5508	1.99
16	2.5059	2.5351	2.5312	2.5429	2.00
17	2.5256	2.5129	2.5526	2.5266	1.68
18	2.5052	2.5226	2.5139	2.5488	2.01
19	2.5259	2.5153	2.5328	2.5306	1.88
20	2.5050	2.5231	2.5414	2.5483	1.71

Standard Deviation

0.0188206 (3.35-0.65)

0.0100949 (3.00-1.00)

0.0231209 (2.00-2.00)

0.0154618 (1.00-2.00)

0.141267756 (Napa 250mg)

Table. 2: Hardness of paracetamol Suppositories in Kg.

S#	3.35-0.65	3.00-1.00	2.00-2.00	1.00-3.00	Napa 250mg
1	7.20 kg	6.85 kg	9.05 kg	9.82 kg	7.50 kg
2	6.10 kg	8.00 kg	7.55 kg	9.26 kg	6.60 kg
3	5.85 kg	6.25 kg	9.25 kg	6.35 kg	7.20 kg
4	5.50 kg	7.35 kg	7.35 kg	8.62 kg	5.89 kg
5	7.23 kg	6.05 kg	8.66 kg	8.96 kg	6.26 kg
6	6.61 kg	8.25 kg	9.31 kg	7.21 kg	7.53 kg
7	7.55 kg	6.35 kg	7.34 kg	9.10 kg	7.51 kg
8	7.23 kg	7.80 kg	8.26 kg	8.32 kg	7.01 kg
9	5.82 kg	6.20 kg	9.02 kg	7.23 kg	6.66 kg
10	7.59 kg	7.10 kg	8.15 kg	9.65 kg	7.35 kg
11	7.01 kg	7.91 kg	9.05kg	9.11 kg	6.86 kg

12	6.26 kg	6.85 kg	9.25kg	8.03 kg	7.01 kg
13	6.89 kg	8.20 kg	7.85kg	7.66 kg	7.52 kg
14	7.53 kg	6.52 kg	8.32kg	7.98 kg	6.83 kg
15	5.99 kg	7.81 kg	8.66kg	8.88 kg	6.66 kg
16	7.51 kg	8.01 kg	7.60kg	6.81 kg	7.12 kg
17	6.66 kg	6.38 kg	9.18kg	8.39 kg	6.70 kg
18	5.96 kg	7.99 kg	7.39kg	9.55 kg	6.88 kg
19	5.60 kg	6.32 kg	8.55kg	7.86 kg	6.61 kg
20	7.35 kg	8.13 kg	9.01kg	7.06 kg	7.01 kg
Average	**6.672 kg**	**7.216 kg**	**8.44 kg**	**8.273 kg**	**6.93kg**

Table No.3: Melting Time of paracetamol suppositories Melting Time.

S#	Name of Product	Ratio	Melting Time at 37°C
1	Paracetamol Suppository	3.35-0.65	1) 27 minutes 2) 27 minutes
2	Paracetamol Suppository	3:00 – 1:00	1) 37 minutes 2) 37 minutes
3	Paracetamol Suppository	2:00 – 2:00	1) 1 hour 2) 58 minutes
4	Paracetamol Suppository	1:00 – 3:00	1) 1hour 15 minutes 2) 1 hour 16 minutes
5	Marketed Suppository	(NAPA 250 mg)	1) 28 minutes 2) 28 minutes

Table No. 4: Dissolution test of Paracetamol suppositories.

Sample Time	% DRUG RELEASE				
Time	**3.35-0.65**	**3.00-1.00**	**2.00-2.00**	**1.00-3.00**	**Napa 250mg**
0 minute	0.00	0.00	0.00	0.00	0.00
5 minutes	10.16	10.37	10.16	10.06	12.57
10 minutes	21.48	20.85	19.39	18.23	23.79
15 minutes	42.97	42.34	41.19	40.35	43.71
20 minutes	69.28	67.29	65.19	64.36	69.70
25 minutes	86.89	84.90	83.12	80.39	85.84
30 minutes	99.05	98.53	97.79	96.33	99.26
35 minutes	98.53	98.11	97.16	95.91	98.95
40 minutes	98.42	97.69	96.75	95.28	98.63
45 minutes	97.69	97.16	96.43	94.86	98.13
50 minutes	97.06	96.64	96.12	94.54	97.69
55 minutes	96.54	96.12	95.80	94.12	97.37
60 minutes	96.22	95.80	95.28	93.92	97.06

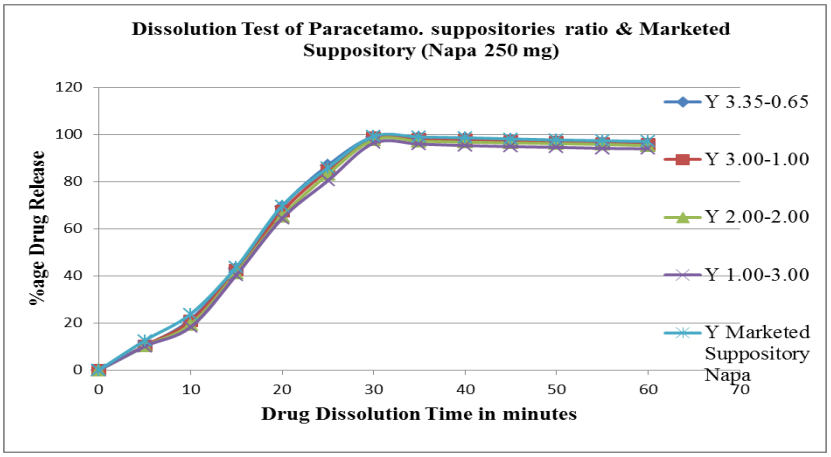


Figure No.1.

Units and Symbols - The use of the International System of Units (SI) is recommended.

Physical quantity	Base unit	SI Symbol
Mass	gram	g
	kilogram	kg
	microgram	µg
Time	second	s
	minute	min
Mass	gram	g
	kilogram	kg
	microgram	µg
	hour	h
Volume	liter	l
	milliliter	ml
	micro liter	µl
	temperature	˚C

DISCUSSION

Paracetamol is widely used as antipyretic and analgesic.When used in the form of suppository it produces rapid effect due to quick absorption through the rectal route.It is similar in efficacy to aspirin but with no demonstrable anti-inflammatory activity.Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 2 to 3 hours after rectal administration. Usual analgesic doses produce total serum concentrations of 5 to 20mcg/ml.

Weight variation (gms) ofparacetamol suppositories from all different ratios (n=20) was determined.No suppositories showed deviated from average weight by more than 5% .The average weight variation of ratio 3.35-0.65 is 2.5168 ± 0.01088206 (n=20),for ratio 3.00-1.00 is2.5193 ± 0.0100949 (n=20) , for ratio 2.00-2.00 is 2.5308 ± 0.02312097(n=20) , for ratio

1.00-3.00 is 2.5378 ± 0.0154618 (n=20), and marketed suppositories (Napa) is 1.83 ± 0.1412677 (n=20).The present study is in the confirmation with the work Ilomuanya Margaret et, al 2012 (22), who reported that weight variation of paracetamol suppositories in different ratio was not more than 5%.Therefore the weight of variation of different suppositories ratio should be in following ranking.

1.00-3.00 > 2.00-2.00 >3.00-1.00 > 3.35-0.65 > Marketed suppositories (Napa).

Hardness test is performed to determine the tensile strength of the suppositories to assess whether they will be able to withstand the hazards of packing and transporting. No suppositories showed deviationfrom average hardness by more than 5%.The average hardness (kg) for ratio (3.35-0.65) is 6.67 ± 0.72498 (n=20), forratio (3.00-1.00) is7.21 ± 0.80304, for ratio (2.00 -2.00) is8.44 ± 0.71112 (n=20) , for ratio (1.00 -3.00) is 8.27 ± 0.98814 (n=20), and marketed suppositories (Napa) is 6.93 ± 0.43717(n=20).The present study is in the confirmation with the work Shegokar Ranjitaet, al 2010 (26), who reported that hardnessof paracetamol suppositoriesin different ratio was not more than 5%. Therefore the average hardness of different suppositories ratio showed the following ranking.

2.00-2.00 > 1.00-3.00 > 3.00-1.00 > Marketed suppositories (Napa) > 3.35-0.65.

Melting time of paracetamol suppositories from different ratios at body temperature, i.e.37°C was determined (n=2).For the ratio (3.35-0.65) melting time at 37°C is 27 minutes ,for the ratio (3.00-1.00)melting time at 37°C is 37 minutes, for the ratio (2.00 -2.00) melting time at 37°C is 1 hour, for the ratio (1.00 -3.00) melting time at 37°C is 1hour and15 minutes, and marketed suppositories (Napa) melting time at 37°C is 28 minutes.The present study is in the confirmation with the work of Shegokar Ranjitaet, al 2010 (26) ,who reported that melting time of paracetamol suppositories is 39 minutes.The melting time of paracetamol suppositories ratio (3.35-0.65) is ideal, i.e, less than 30 minutes. Therefore the average melting time of different suppositories ratio showed the following ranking.

3.35-0.65> Marketed suppositories (Napa) > 3.00-1.00 > 2.00-2.00 > 1.00-3.00.

The % release of drug of paracetamol suppositories from different ratios at body temperature i.e. 37°C was determined (n=1).The ratio 3.35-0.65 (99.05%) drug is released in 30 minutes,for ratio 3.00-1.00 (98.53%) drug isreleased in 30 minutes, for ratio 2.00 -2.00(97.79%) drug is released in 30 minutes, for ratio 1.00 -3.00 (96.33%) drug is released in

30 minutes and marketed suppository (Napa)(99.26%) drug isreleased in 30 minutes .The present study is in the confirmation with the work Shegokar Ranjitaet, al 2010 (26).Therefore the dissolution time of different suppositories ratio showed the following ranking.

Napa suppositories > 3.35-0.65 > 3.00-1.00 > 2.00-2.00 > 1.00-3.00.

CONCLUSION

On the basis of present study it can be concluded that paracetamol suppositories of the ratio 3.35 -0.65 is good as compared to other ratio of different paracetamol suppositories.The ratio 3.35-0.65; which matches the results obtained from marketed suppository (Napa).

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