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Effect of Adjuvants on the Release Pattern of Suppositories Containing Paracetamol

Niraj Gupta^{1*}, Shweta Pandey¹, HM Varshney¹, M.M Gupta¹.
1. Jaipur College of Pharmacy, Jaipur, Rajasthan-302022, India

ABSTRACT

There is a vast interest in the scientific community and drug industry to exploit various mucosal routes of delivering drugs, which are poorly absorbed after oral administration. Human rectum remains to be a relatively unexplored route of drug delivery despite its potential as a non-invasive route of drug administration. The presence of dense network of blood vessels has made the rectum an excellent route of drug delivery for both systemic and local effect. The present investigation was aimed to evaluating the possibility of using different surfactant i.e. Span 60 and 80, Tween 60 and 80 on the release rate of formulation for the development of rectal drug delivery system of paracetamol, an NSAIDs, to minimize the gastric irritation of the drug upon oral administration. Suppositories were formulated by fusion method & evaluated for their physicochemical characterization followed by *in vitro* evaluation through spectrophotometrically. Suppositories containing PEG 4000 with Tween 80 showed a better permeation of drug with faster dissolution rate *in vitro* than other formulations. The formulations were designed to overcome the risk of upper gastrointestinal complications such as stomach bleeding, and may cause kidney or liver damage. Suppositories are dosage forms for use in the unavoidable circumstances such as comatose, nauseous or vomiting.

Keywords: Paracetamol, PEG 4000, Tween 60, Tween 80, Span 60, Span 80, PEG 400

*Corresponding Author Email: hmv_mpharm2005@yahoo.com

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INTRODUCTION

Various factors including drug solubility in the base, the chemical composition of the base and drug particle size are responsible for drug release from a number of suppository bases. The drug release from the suppositories bases is influenced by the presence of other additives in the formulation and may result in an increase or decrease in the rate of release depending on the nature of the base and that of the additives and its concentration ¹.

Non-steroidal Anti-inflammatory Drugs (NSAIDs) are usually good candidates for the development of controlled release preparations particularly through the rectal route to reduce or eliminate the gastrointestinal irritation. Paracetamol is an NSAID having prominent anti-inflammatory, analgesic and antipyretic properties. Similar to other NSAIDs paracetamol also exerts its therapeutics effects largely by its ability to inhibit the biosynthesis of prostaglandins in all cells through inhibition of cyclooxygenase, thus inhibiting the gastro-protective prostaglandin's which leads to gastric intolerance ². Absorption after rectal doses may be more rapid. It is bound to plasma proteins and has a plasma half-life of about 1–4 hours. Glucuronidation is believed to account for 40% to two-thirds of the metabolism of paracetamol. Sulfation (sulfate conjugation) may account for 20–40%. Generally, drug release from a number of suppository bases depends upon the drug solubility in the base, the chemical composition of the base and drug particle size. The drug release from the suppositories bases is influenced by the presence of other additives in the formulation and may result in an increase or decrease in the rate of release depending on the nature of the base and that of the additives and its concentration³. There are reports describing attempts at enhancing the rate of release of drug from different suppository bases by incorporation of surfactants.

The objective of the study is to develop suppository of paracetamol by incorporation of suppository base and different surfactants with a view to avoid loss of drug due to first pass effect and to uncover toxic effects and produce safe and effective dosage form and safely improve the solubility, bioavailability and/or absorbability of poorly soluble drug.

MATERIALS AND METHODS:

Paracetamol was a gift sample from Sun Pharmaceutical Industries Ltd., Silvassa, Gujarat, & FDC Limited, Jogeshwari (w), Mumbai, Poly ethylene glycol 4000 and 400 were purchased from Central Drug House (P) Ltd., New Delhi. Cocoa butter (B.P.grade) was purchased from Mohan Scientific & Pharmaceuticals, New Delhi. Sodium lauryl sulphate was purchased from S.D. Fine Chem. Ltd., Mumbai. All other chemicals and reagents were used of analytical grade.

Preparation of Paracetamol Suppositories

Accurately weighed quantities of respective suppositories bases were melted on the water bath. The finely divided drug powder and surfactants (1 % w/w of suppositories bases) were incorporated via through mixing. Paraffin wax was used as lubricant. The melted mass was poured into the appropriate suppository mould (1.0 g capacity). For suppositories with surfactant and plasticizer (PEG 400) (20% w/w of suppositories bases) used. The suppositories were then refrigerated ⁸, they were stored at 4 °C to avoid the development of cracking ⁴and exposure to room temperature was limited to less than 24 h before use in *in vitro* release studies (Figure 1).

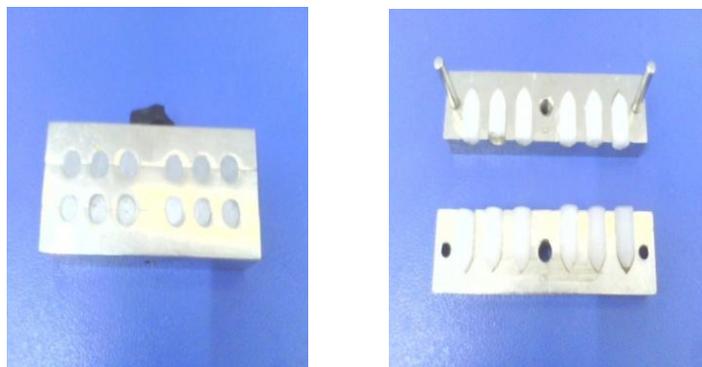


Figure 1. Suppository mold used in formulating suppositories in (a) closed &(b) open position, allowing removal of the finished hard suppositories after cooling.

Table 1. Code and composition of the formulations

Code	Suppository base* (gm)PEG 4000	Drug (Paracetamol)(mg)	Surfactants (gm)	Plasticizer (PEG 400)(gm)
F1	0.990	100	-	-
F2	0.979	100	0.011	-
F3	0.979	100	0.011	-
F4	0.979	100	0.011	-
F5	0.979	100	0.011	-
F6	0.659	100	0.011	0.22
F7	0.659	100	0.011	0.22
F8	0.659	100	0.011	0.22
F9	0.659	100	0.011	0.22

*Based on mould capacity

Characterization of Suppositories

Subsequent to suppository development and manufacture, the finished product must undergo a number of simple tests in order to ascertain quality. Ideally, these tests should be repeated periodically during storage as well.

The visual parameters such as fissuring, pitting, fat blooming, exudation, migration of active ingredient and physical parameters such as length, width, weight variation, hardness (mechanical

strength), breaking strength, liquefaction time, melting time of prepared suppositories were determined.

VISUAL CHARACTERIZATION

The randomly selected suppositories (six suppositories from each batch) were cut longitudinally and examined with the naked eye (subjective evaluation) to assess the verified the homogeneity of surface appearance and color of suppositories by Absence of fissuring, Absence of pitting, Absence of fat blooming, Absence of exudation, Absence of migration of the active ingredients. This last test is best accomplished by taking a longitudinal section of the suppository to verify the homogeneity of the active ingredient(s) within the mass².

Length and Width

The width and length of the randomly selected suppositories (six suppositories from each batch) were measured for their physical dimension. After that the same number of suppositories were selected and cut longitudinally and the surface was examined with the naked eye (subjective evaluation) for the homogeneity¹³.

Breaking Strength

The breaking strength or crushing strength was determined for measuring fragility or brittleness of suppositories, which assess whether the suppositories will be able to withstand the hazards of packing, transporting and normal handling or not (Moorthi et al. 2005, Gulzar et al. 2000).



Figure 2. Breaking strength measurement of prepared suppository by Erweka tester.

A plastic disc was fixed horizontally on to one end of the iron rod to which weight are applied and other end had been reduced to sharp point. The sample suppository was placed between the metal plate and the sharp end of the iron rod and placing 200 g weights on to the pan. At 1-minute intervals, 50 g weights are added, and the weight at which the suppository collapses in the breaking point, or the force that determined the fragility of brittleness characterization of the suppositories¹¹.

Mechanical Strength (Hardness)

A physical characteristic such as mechanical strength (hardness test) was determined. The hardness of a cylindrical portion (9.6 mm thickness) of suppository, which was obtained by

cutting the middle portion of the suppository, was measured in its diameter direction with a Monsanto hardness tester⁷.

Weight Variation

Twenty suppositories were weighed and average weight was calculated. Each suppository was then individually weighed by using digital balance¹³. Not more than 2 of the individual masses deviate from the average mass by more than 5 % and non deviate by more than twice that %¹⁵.

Friability

Twenty suppositories were weighted and placed in the plastic chamber of Roches Friabilator (Figure 3). The chamber was then rotated for 4 minutes at 25 rpm (a total of 100 revolutions). During each revolution suppositories fall from a distance of 6 inches. After 100 revolutions the suppositories were removed and weighed again.

$$\text{Friability (\%)} = \frac{W_i - W_r}{W_i} \times 100$$

Where, W_i was the initial weight of the suppositories before friability testing, W_r was the weight of suppositories after the testing¹¹.



Figure 3 Roches Friabilator for measuring of friability of prepared suppository.

Melting Point

The melting time is a critical factor in the determination of the release rate of the active ingredient(s) from the suppository. This test is also known as macro melting range test. During this test, the time taken for the entire suppository to melt or disperse is measured when immersed in a water bath maintained at constant temperature ($37^{\circ}\text{C} + 1^{\circ}\text{C}$). The time required for the whole suppository to melt or disperse in the surrounding water was noted^{7,9,12,13}.

Liquefaction or Softening Time

This important element indicates the physical behavior of a suppository subjected to its maximum functional temperature (37°C) (2). It consists of a U-tube partially submersed in a constant temperature water bath. A constriction on one side holds the suppository in place in the tube. An iron rod is placed on the top of the suppository and the time for the rod to pass through to the constriction is recorded as the “softening time”. This can be carried out at various

temperatures from 35.5 to 37 °C, as a quality control check and can also be studied as a measure of physical stability over time. The softening test measures the liquefaction time of rectal suppositories¹¹. In this, to measures the time necessary for a suppository to liquefy under pressure similar to those found in the rectum in the presence of phosphate buffer pH 7.4 (5.0 ml) surrounding the water at body temperature².

Content Uniformity

Content uniformity test was determined by spectrophotometric method. The suppository was individual melted, dissolved in 100 ml of PBS (pH 7.4 buffer) in separate volume flask and the solution was filtered using 0.45 µm membrane. After suitable dilution, the absorption was measured using thermospectronic UV-1 at a wave length of 247 nm^{7,12,13}.

Dissolution Study

The USP basket method was employed for all the *in vitro* dissolution studies (USP-XXVI, Veego Scientific, Mumbai). In this method 900 ml of Phosphate buffer solution pH 7.4 was used as the dissolution medium. The rate of stirring was 100 rpm. The suppositories were placed in basket and the temperature of the dissolution medium was maintained at 37°C + 1°C for a period of 150 minute. All different time intervals 1 ml of the sample was taken and filtered. The dissolution medium was the replaced by 1 ml of fresh dissolution fluid to maintain a constant volume. The samples were filtered through 0.45 µ membranes, diluted suitably and assayed at 247 nm using a UV-visible spectrophotometer (Thermospectronic UV-1)^{4,10}.

RESULT AND DISCUSSION

Paracetamol is an analgesic and non-steroidal anti-inflammatory drug usually employed in analgesic and antipyretic. It is rapidly eliminated from the blood after dosing administration. It has a plasma half life of 1-4 h and to maintain the therapeutic plasma levels. Prolonged daily use increases the risk of upper gastrointestinal complications such as stomach bleeding, and may cause kidney or liver damage. Paracetamol is metabolized by the liver and is hepatotoxic; side effects may be more likely in chronic alcoholics or patients with liver damage.

Suppositories of Paracetamol were prepared by fusion method employing suppository base i.e. PEG 4000. The results of visual and physicochemical characterization are shown in Table 2 and 3. All the formulations were found to have homogeneous drug distribution with content uniformity, weight uniformity and sufficient mechanical strength to withstand abrasive forces causing disintegration of drug loaded formulation. The width and length of the randomly selected suppositories was found to be good homogeneity. The crushing or breaking strength was

determined for measuring fragility or brittleness of the suppositories, which assess whether the suppositories will be able to withstand hazards of packaging, transporting and normal handling or not. The formulated rectal suppositories were smooth and fine in texture with mechanical strength (hardness) i.e. all the formulae could tolerate less than 5 kg. The weight variations were conformity with the British Pharmacopoeia for each formula, with standard deviation of less than 5 %. The friability was found to be within acceptable limits (less than 1 %). With respect to melting range, the suppositories with or without surfactants containing Paracetamol can be arranged in the order of F5 > F4 > F2 > F9 > F6 > F7 > F3>F8>F1. The liquefaction time was studies as a measure of physical stability over time. The estimation of drug content in the formulation revealed that the drug was distributed uniformity with low coefficient of variations, indicating batch to batch consistency. Considering the drug content uniformity test, the difference between mean of each formula and the theoretical values was less than 10 %. All standard deviation were less than 5 %. The drug content of all the formulations was determined spectrophotometrically at 247 nm. It varied from 94.12% to 97.46 % per suppository.

Table 2. Visual characterization of the formulations

Code	Fissuring	Pitting	Fat blooming	Exudation	Migration of active ingredient	Length (cm)	Width (cm)
F1	NO	NO	NO	NO	NO	2.1±0.009	0.8±0.004
F2	NO	NO	NO	NO	NO	2.2±0.009	0.9±0.004
F3	NO	NO	NO	NO	NO	2.2±0.009	0.9±0.004
F4	NO	NO	NO	NO	NO	2.1±0.009	0.9±0.004
F5	NO	NO	NO	NO	NO	2.2±0.009	0.9±0.004
F6	NO	NO	NO	NO	NO	2.1±0.009	0.9±0.004
F7	NO	NO	NO	NO	NO	2.1±0.009	0.9±0.004
F8	NO	NO	NO	NO	NO	2.1±0.009	0.9±0.004
F9	NO	NO	NO	NO	NO	2.1±0.009	0.9±0.004

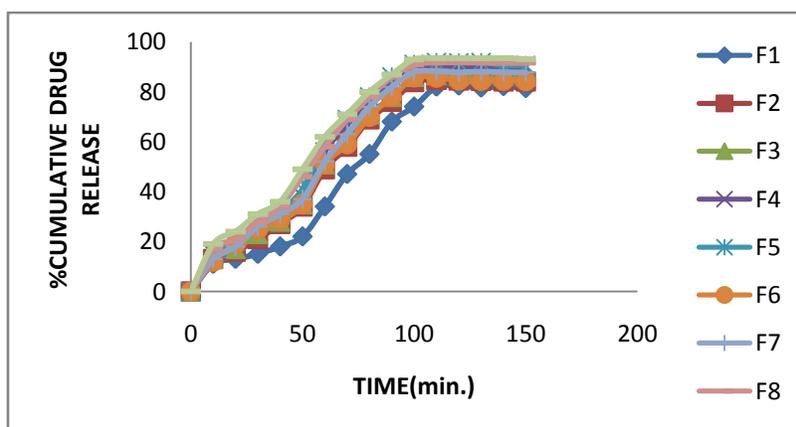
Table 3. Physico-chemical characterization of the formulations

Code	Weight variation (mg)	Friability (%)	Hardness (kg/cm ²)	Breaking strength (gm)	Liquefaction time (min.)	Melting time (min.)	Drug Content (mg)
F1	1.1±0.0029	0.35±0.02	2.3	423±15.2	1:20±0:0003	22:10±0:023	95.88
F2	1.16±0.004	0.42±0.02	2.5	428±15.2	1:32±0:0015	24:18±0:015	96.32
F3	1.12±0.004	0.44±0.02	2.4	430±15.4	1:39±0:0007	25:23±0:036	96.89
F4	1.11±0.003	0.48±0.04	3.1	435±16.2	1:46±0:0024	26:24±0:043	97.46
F5	1.24±0.004	0.47±0.04	3.8	438±16.4	1:43±0.0037	26:38±0:011	97.15
F6	1.21±0.003	0.51±0.02	2.1	442±15.4	1:38±0.0009	27:20±0:029	95.44
F7	1.22±0.003	0.51±0.02	2.3	444±15.4	1:41±0.0022	27:42±0:044	94.12
F8	1.33±0.004	0.53±0.04	2.7	446±16.2	1:47±0.0032	27:55±0:031	96.09
F9	1.33±0.004	0.53±0.04	2.9	448±16.2	1:42±0.0019	28:10±0:008	96.56

Table 4. Cumulative drug release of the formulations

%Cumulative drug release									
Time(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
10	11	13	13	15	16	12	13	17	19
20	13	16	17	19	20	19	18	21	24
30	15	21	23	26	28	25	26	28	31
40	18	27	28	31	32	29	31	34	36
50	22	34	35	38	41	35	37	46	49
60	34	49	51	56	59	51	52	58	62
70	47	58	62	67	69	59	63	69	71
80	55	69	71	76	78	70	74	78	80
90	68	76	78	84	86	78	82	86	87
100	74	84	86	90	91	85.8	88	91	93
110	82	84.8	86.7	90.4	91.8	85.7	88.2	91.7	93.5
120	82.4	84.6	86.5	90.2	91.7	84.6	87.8	91.8	93.5
130	81.6	84.4	86.5	90.2	91.8	84.4	88.1	91.7	93.4
140	82.2	84.2	86.4	89.8	90.6	84.4	87.9	91.6	93.5
150	81.4	84.2	86.2	89.7	90.6	84.3	87.8	91.6	93.1

The release profile from different suppositories formulations are shown in Figure 3. Percentage cumulative drug releases from suppositories of PEG 4000 and with different adjuvants were found to be 82.0, 84.8, 86.7, 90.4, 91.8, 85.7, 88.2, 91.7 and 93.5% respectively at the end of 150 minutes. It was found that the Tween 80 with plasticizer should maximum release of Paracetamol from suppositories followed by PEG 4000 and with different surfactants.

**Figure 3. In vitro dissolution of Paracetamol from different suppositories**

CONCLUSION

The type of the adjuvants employed for the preparation of suppositories of paracetamol, influenced the release of the drug during the dissolution studies and dependent upon the condition. It may be concluded that the addition of adjuvants into the formulation enhanced the drug release and with respect to adjuvants, can be arranged as- Tween 80+PEG 400

(plasticizer)> Tween 60+PEG 400 > Span 80 +PEG 400 > Span 60+PEG 400 > Span 80 > Span 60 > Tween 60> Tween 80.

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