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SHOREA ROBUSTA BUTTER AS NOVEL AND NATURAL SUPPOSITORY BASE FOR FORMULATION AND EVALUATION OF MULTILAYERED RECTAL SUPPOSITORIES

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ABSTRACT

The rectal route though rarely the first choice of drug administration serves as an alternative to oral and invasive administration. Rectal drug delivery is so pivotal when the oral medication is not possible, intra venous access is not possible and the patients have difficulty in swallowing, nausea and vomiting and for infants or children. Suppository prepared from the novel natural base is attracting considerable attention for rectal drug delivery. They are renewable, economic, easily available, nontoxic and have its own medicinal properties In the present investigation an attempt has made to formulate multilayer suppository incorporating herbal base I.e. *Shorea robusta* butter. Suppositories were fabricated by *Shorea robusta* butter as base and Levodopa and Selegilline as drug by using pour molding method. From the studies it was found that the Sal fat suppositories had good appearance, good mechanical strength and good drug release properties. Above all it remains solid at room temperature and possess the melting temperature in the range of 30 – 36℃ which is an important prerequisite of any suppository base. The stability studies also revealed the satisfactory results. The studies suggested that Sal fat may be used as a base for conventional immediate release suppositories as it has been found that it possesses all the characteristics as possessed by ideal suppository base.

KEYWORDS: Suppository, *Shorea robusta* butter, pour molding, prerequisite, ideal suppository base.

INTRODUCTION

Suppositories are solid dosage forms intended for insertion into body orifices (rectum, vagina, urethra) where they melt, soften, or dissolve and exert a local or systemic effect.[1] Rectal suppositories intended for localized action are most frequently used to relieve constipation or pain, irritation, itching and inflammation associated with hemorrhoids and Systemic action: (e.g. Antiasthmatic, antirheumatic & analgesic drugs).

Properties of Ideal Suppository Base

The properties of an ideal suppository base:

- Melts at body temperature or dissolves in body fluids.
- Non - toxic and non - irritant.
- Compatible with any medicament.
- Releases any medicament readily.
- Easily molded and removed from the mold.
- Stable to heating above the melting point.
- Stable on storage

Shorea robusta (Sal), botanical family – Dipterocarpaceae is an important traditional Indian medicinal plant used in various ailments and rituals and the indigenous use of the resin of this plant as a medicament for treatment of various inflammatory conditions is well documented in literature.[2] From its fruit kernels the butter is extracted and further processed and refined to obtain a light colored butter which has a low odor and smooth, dense texture, suitable for cosmetics and toiletries. It contains mostly C18:0 and C18:1 fatty acids. Shorea Butter is solid at room temperature, but melts readily upon contact with the skin. It has physical properties similar to cocoa butter; however, it may be used in higher quantities to provide stable emulsions due to its uniform triglyceriede composition, along with a high oxidative stability. Also exhibits excellent emolliency properties, softening effects and good spreadability on the skin.[3]

Suggested uses[2]: Lotions & Creams: 4 - 8%, Balms: 7 - 100%, Bar Soaps: 3 - 6%, Hair Conditioners: 3 - 7%, Efficacy[3]: Exceptionally good oxidative stability due to very low content of polyunsaturated fatty acids. Prevents drying of the skin and development of wrinkles. Reduces degeneration of skin cells and restores skin flexibility.

Multilayered Suppositories

It is suppository containing two compatible or incompatible drugs having middle separating layer of blank base. More than two drugs can also be used in these type of suppositories. Multilayered suppositories are suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release formulations in which one layer is immediate release as initial dose and second layer is maintainance dose.

Multi – layer suppositories are designed for variety of reasons.[4]

- To control the delivery rate of either single or two different active pharmaceutical ingredient(s)
- To separate incompatible Active pharmaceutical ingredient (APIs) from each other,
- To control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property).
- To modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable /erodible barriers for modified release.
- To administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery system.
- To reduce the numbers of medicines administered at a time.

Parkinson's Disease[5]

Parkinson's disease is a chronic progressive neurodegenerative disorder of insidious onset, characterized by the presence of predominantly motor symptomatology (bradykinesia, rest tremor, rigidity, and postural disturbances). It is also associated with a diversity of non - motor symptoms, which, together with late - onset motor symptoms (such as postural instability and falls, freezing of gait, speech and swallowing difficulties).

Treatment

Therapeutic concentration of the drug must be maintained for optimal seizure control in both acute and chronic treatment of Parkinson. When chronic administration of medication is required but due to lack of oral access and incompatibility of IV formulation of medication alternative routes of drug dosing is required. Importance of rectal route in anti parkinson drug administration is partial avoidance of first pass metabolism. Diazepam by rectal route as solution and gel preparation has been used for several decades for treating repetitive or

prolonged seizures in children. Diazepam solution administered rectally result in rapid and complete absorption with peak plasma concentration attained within 5 - 15 min.[6]

L - DOPA crosses the protective blood brain barrier, whereas dopamine itself cannot. Thus, L - DOPA is used to increase dopamine concentrations in the treatment of Parkinson's disease and dopamine - responsive dystonia. Once L - DOPA has entered the central nervous system, it is converted into dopamine by the enzyme aromatic L - amino acid decarboxylase, also known as DOPA decarboxylase.

Selegiline is a selective inhibitor of MAO - B; MAO-B metabolizes dopamine and phenylethylamine. Selegiline exhibits little therapeutic benefit when used independently, but enhances and prolongs the antiparkinson effects of levodopa and reduced 20 - 30% dose of levodopa.

The rectal formulation of Levodopa as a dilute suspension, have been found to be bioequivalent to administration as oral tablets and oral suspension.[7]

In the present investigation an attempt has been made to formulate multilayer suppository by using two drugs with different mechanism of action in a single formulation incorporating herbal base I.e. *Shorea robusta* butter. It is a fatty excipient thus used either alone or with combination with other fatty bases.

MATERIALS AND METHODS

Materials

Material used for the formulation of mulilayered suppository were either laboratory grade or the best possible pharma grade available were used as supplied by the manufacturer without further purification or investigation. Distilled water was used throughout the study.

Levodopa purchased from Swapnroop Chemicals Aurangabad, Selegiline HCL obtained as gift sample from Intas Pharma, Pvt Ltd. Shorea robusta butter is procured from Charbhuja Industry, MIDC Hingna Nagpur-4. Tween 80, Emulsifying Wax, Methyl Paraben and Propyl Paraben were purchased from Loba chemie, Pvt. Ltd, Mumbai 6.

Equipments

UV - Visible spectrophotometer – Shimadzu (UV 1601 Shimadzu Corporation, Japan), used for scanning of drug and drug release. Magnetic stirrer (Remi Equipments, Mumbai), used for

drug content study. High Precision Balance (Wensar, PGB200 Mumbai), for weighting of drugs and excipients. pH meter (Electonic India, 181 E, Ambala), used for estimation of pH. FT – IR Shimadzu (FT - IR Shimadzu Corporation, Japan), used for compatibility studies. Dissolution Test Apparatus(8 Stage) (Veego – VDA - 8D USP, Mumbai), for drug release studies. Melting Point Apparatus (Kumar, 181, Mumbai), used for determination of melting point.

Methods

Suppositories were fabricated by pour molding method.[8]

The mold was calibrated with Sal fat before preparation of suppositories. Displacement value was calculated. Accurately weighed quantity of emulsifying wax was melted on the water bath maintained at 50˚C, required quantity of Sal fat was added and allowed to melt. Tween 80 in specific proportion was added. Methyl paraben and propyl paraben was added to this mixture as preservative and allow it to cooling for 10 minutes. Accurately weighed quantity of above base, melt it and mix accurate amount of selegiline. The melt was then poured into previously calibrated, lubricated and cooled stainless steel suppository mold. The mold was set aside for cooling for 10 min. Weighed quantity of base was taken in 2nd beaker, melted and pour on the bottom layer as separating layer. Keep in refrigerator for 10 min. Weighed quantity of base was taken in another beaker, melted. Drug levodopa was dispersed in melted base with stirring and poured into the mold above 2nd layer and keep in refrigerator for 10 min. Remove the formulation from mold and wrapped it into aluminium foil and stored it into refrigerator until further analysis. So that each suppository contained levodopa and selegiline.

Preparation of coca butter suppositories

Coca butter Suppositories were also fabricated by pour molding method same as shorea robusta butter suppository.

Evaluation of multilayered suppositories

1. Physical properties[9]

(a) Appearance: This includes odours, colour, surface condition and shape.

(b) Weight uniformity

Three different formulations of each batch were randomly selected and weighed. The average weight was calculated. Then all the suppositories were weighed individually and variation from the average was determined. Not more than two of the individual weights deviated from

the average weight by more than 5% and none deviated by 10%. The weight of each suppository was taken and the weight variation was calculated.

(c) Liquefaction Time or Softening Time Test

Softening and liquefaction time measures the time necessary for suppository to liquefy under pressure similar to those found in the rectum in the presence of water at body temperature.[6]

(d) Melting range test

The prepared suppositories were tested for macro melting range and micro melting range. Macro melting range was determined by measuring the time taken for the entire suppository to melt when immersed in constant temperature bath maintained at 37 ± 0.5℃. Micro melting range test was carried out by using capillary tubes of 10 cm length in which the formulation was filled upto 1cm height and dipped in water bath. The temperature was increased slowly and the temperature at which the mass liquefies was noted.

(e) Breaking Test (Hardness)

Hardness test is carried out to determine the tensile strength of the suppositories. The hardness of the formulated suppositories was tested using Monsanto hardness tester. The hardness test also reveals the ability to withstand the hazards of packing and transportation.[7]

(f) Drug Content

Drug content in Sal fat suppositories was determined by placing one suppository in 200 ml of Phosphate buffer pH 7.2 maintained at 37 ± 0.5℃ till it melted. 1ml of sample was withdrawn and diluted to 100 ml with phosphate buffer pH 7.2. The content of drugs was determined by using UV/ Vis spectrophotometer (Shimadzu 240 1A made in Japan) by measuring absorbance of the diluted sample at suitable wavelength.

(g) Disintegration time

The disintegration time of the suppositories was determined by using USP disintegration test apparatus.[10] The time taken for the disintegration of entire suppository was recorded. Phosphate buffer pH 7.2 maintained at 37 ± 0.5℃ was employed for this testing.

2. *In - vitro* release profile

In - vitro release study was performed by using USP type Dissolution Test Apparatus (8 Stage) Veego – VDA - 8D. The dissolution medium used was 900 ml of distilled water maintained at 37 ± 0.5℃. he suppository was placed in the medium at 50 rpm. 1 ml of sample

was withdrawn every 10 minutes, filtered and analyzed using UV spectrophotometer at specific wave length. The studies were continued for 60 min.[10]

3. Stability studies

The suppositories were also subjected to stability studies. The suppositories were wrapped in the aluminum foil and kept in stressed condition using freeze 2 - 8℃ and thaw (25℃) method. Suppositories were also kept in accelerated condition temperature (30℃) for 45 days. Suppositories were examined visually and drug content was determined on a UV/ Vis spectrophotometer by measuring absorbance at specific wavelength.

RESULT AND DISCUSSION

Characterization of *Shorea robusta* Butter

Table 1: Characterization of *Shorea robusta* butter

Sr. No.	Properties	Reported Value	Observed Value
1	Melting Range	34-38°C	35 – 37°C
2	Solidification Value	32-34°C	34 ± 1°C
3	Saponification value	200-245	224.4 ± 0.2
4	Acid Value	< 0.4	0.4 ± 0.003
5	Ester Value	200-240	224.0 ± 0.2
6	Iodine Value	< 8	7.92 ± 0.021

(Mean ±S.D., n=3).

Physical and chemical evaluations of *Shorea robusta* butter indicates that it have passes the different parameters like Melting point, Solidification value, Saponification value, Acid value, Iodine value and Ester value. All parameters have been found within specified limits.

DSC Studies

DSC thermogram of butter was recorded by sample was placed in aluminum pan with a reference pan heated at a rate of 20^0C / min over a range of 25 - 75˚C. Inert atmosphere was maintained with purge of nitrogen gas.

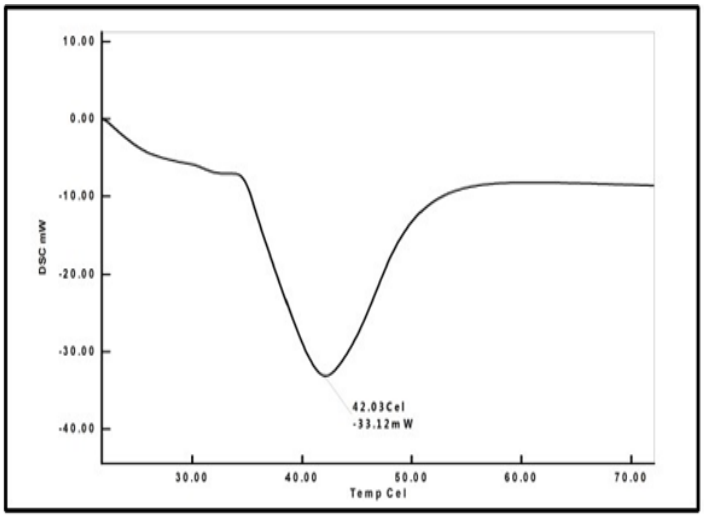

Fig. 1: DSC Thermogram of *Shorea robusta* butter

Compatibility Studies by Fourier Transform Infrared Spectroscopy (FTIR)

Levodopa

IR spectrum of Levodopa revealed the presence of major functional groups present in the structure of Levodopa supporting its identity. IR spectrum indicated characteristic peaks belonging to major functional groups such as principal peaks at wave – numbers 3203.90, 3367.87, 1653.07 and 1458.25 cm^{-1}.

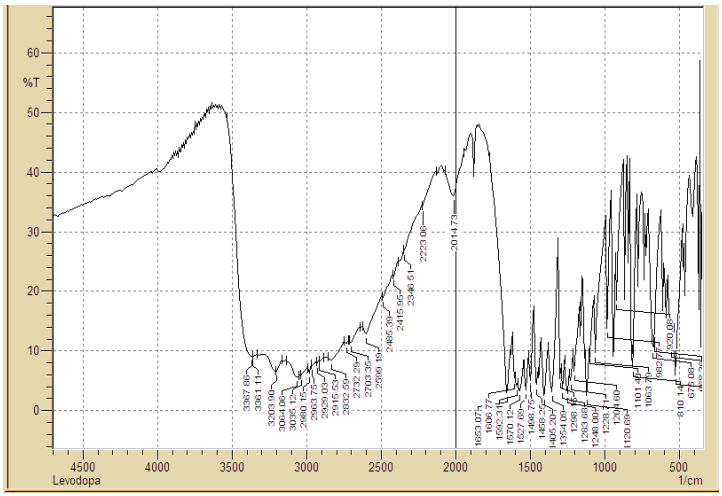

Fig. 2: IR spectrum of Levodopa

Selegiline

IR spectrum of Selegiline revealed the presence of major functional groups present in the structure of Levodopa supporting its identity. IR spectrum indicated characteristic peaks belonging to major functional groups such as principal peaks at wave numbers 3231.87, 2944.46, 2862.49 and 2124.

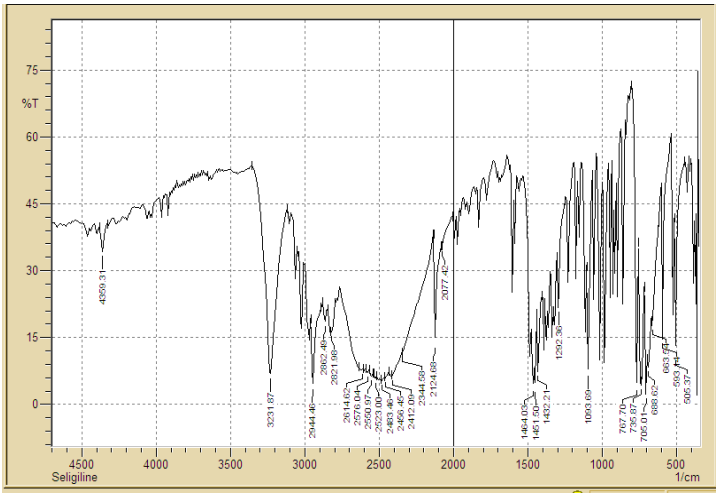

Fig. 3: IR spectrum of Selegiline

Selegiline and S. R. butter

IR spectrum of mixture of Selegiline and S R butter revealed the presence of major functional groups present in the structure of Selegiline supporting its identity. IR spectrum indicated characteristic peaks belonging to major functional groups such as principal peaks at wave numbers 3231.87, 2944.46, 2862.49 and 2124. Thus butter do not change the structure of drug, and it is compatible with drug.

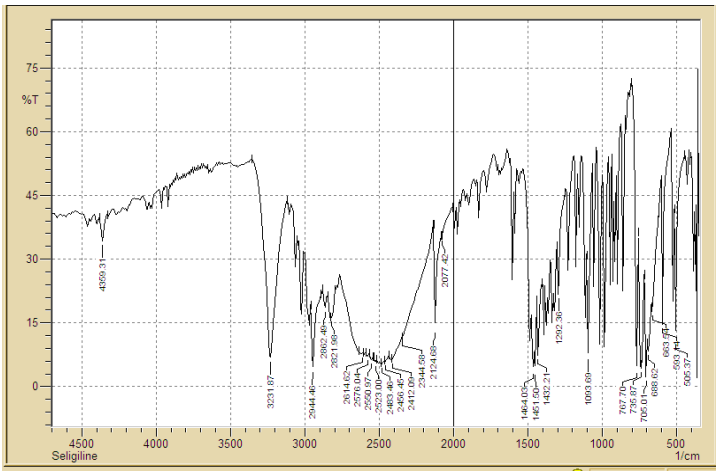

Fig. 4: IR spectrum of mixture of Selegiline and S R butter

Levodopa and S. R. butter

IR spectrum of mixture of levodopa and S R butter revealed the presence of major functional groups present in the structure of levodopa supporting its identity. IR spectrum indicated characteristic peaks belonging to major functional groups such as principal peaks at wave – numbers 3203.90, 3367.87, 1653.07 and 1458.25cm^{-1}. Butter do not change the structure of levodopa thus it is compatible with levodopa.

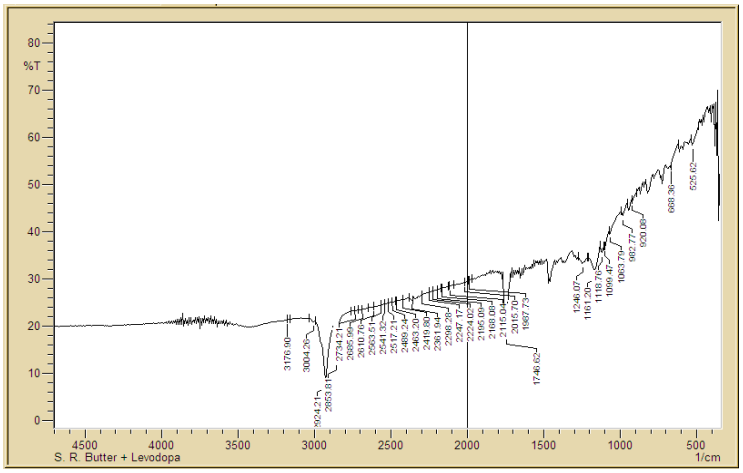

Fig. 5: IR spectrum of mixture of levodopa and S R butter

Formulation and optimization of formula for *Shorea robusta* suppositories

The multilayered suppositories were prepared by pour molding method by using *Shorea robusta* butter, different concentrations of emulsifying wax and tween 80 with two different drugs i.e. Selegiline and Levodopa. Methyl and propyl paraben are used as preservatives. Total 5 formulations were prepared i.e. batch S1 to S5.

Table 2: Formulation Table for *Shorea robusta* suppositories

Sr. No.	Formulation code	S1	S2	S3	S4	S5	C1
1.	Levodopa (mg)	500	500	500	500	500	500
2.	Selegiline (mg)	10	10	10	10	10	10
3.	Emulsifying wax (mg)	_	100	200	300	400	_
4.	Methyl paraben (mg)	1.5	1.5	1.5	1.5	1.5	1.5
5.	Propyl paraben (mg)	1.0	1.0	1.0	1.0	1.0	1.0
6.	Tween 80 (mg)	100	_	200	350	500	_
7.	*Shorea robusta* Butter	qs	qs	qs	qs	qs	_
8.	Coca Butter	_	_	_	_	_	qs

Evaluation of Suppositories

Physical properties

Table 3: Evaluation of Suppositories for Various Parameters

Sr. No.	Parameter	S1	S2	S3	S4	S5	C1
1	Wt Uniformity (gm)	1.99±0.006	2.0±0.002	2.1±0.002	2.1±0.002	2.2±0.002	2.2±0.002
2	Soft. Time (min) at 37 ° C	0.05±0.001	3.5±0.002	1.0±0.002	1.5±0.001	2.5±0.001	3.0±0.002
3	Hardness Test (gm cm^2)	2.4 ± 0.02	6.3 ± 0.03	3.3 ± 0.02	4.0 ± 0.01	3.5 ± 0.02	4.5 ± 0.1
4	Melting Range (°C)	35 ± 0.002	38± 0.001	36± 0.003	36 ±0.001	37±0.002	36±0.002
5	Drug content (%)	98.5±0.02	97.8±0.01	98.9±0.02	98.2±0.03	98.9±0.03	98.6±0.02
6	Disintegration Time (min)	3 ± 0.002	7 ± 0.003	4.5±0.002	5 ± 0.003	5 ± 0.002	4.5±0.001

(Mean ±S.D., n=3).

***In – Vitro* Drug Release Studies**

Table 4: In – vitro drug release of Levodopa (Cumulative % Drug Release)

Time (min)	S1	S2	S3	S4	S5	C1
0	0.00	0.00	0.00	0.00	0.00	0.00
10	8.17 ± 0.85	8.98 ± 0.77	6.70 ± 0.67	7.77 ± 0.69	8.58 ± 0.85	5.50 ± 0.98
20	16.89 ± 0.65	18.22 ± 0.67	16.08 ± 0.85	16.35 ± 0.69	20.10 ± 1.04	12.06 ± 0.85
30	35.78 ± 0.78	32.44 ± 0.58	30.89 ± 0.98	27.61 ± 0.85	37.93 ± 0.98	19.17 ± 0.99
40	46.67 ± 0.67	43.99 ± 0.98	45.18 ± 0.64	43.31 ± 0.63	52.83 ± 0.69	37.80 ± 0.67
50	60.91 ± 0.89	66.66 ± 0.85	64.78 ± 0.69	56.74 ± 0.98	59.98 ± 0.67	56.32 ± 0.64
60	68.21 ± 0.56	72.09 ± 0.64	71.55 ± 0.85	68.46 ± 1.02	74.24 ± 0.85	75.13 ± 0.98
70	73.77 ± 0.98	77.93 ± 0.95	78.32 ± 0.66	80.98 ± 0.44	85.44 ± 0.64	81.90 ± 0.67

(Mean ±S.D. n=3).

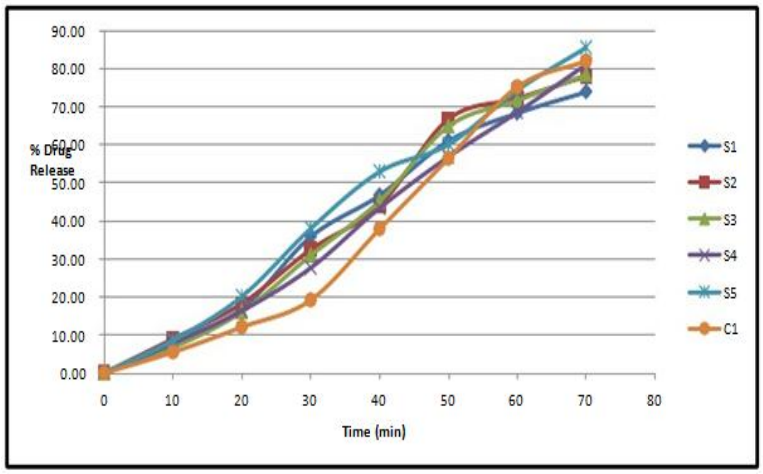

Fig. 6: *In – vitro* drug release of Levodopa

Table 5: In – vitro Drug Release of selegiline (Cumulative % Drug Release)

Time (min)	S1	S2	S3	S4	S5	C1
0	0.00	0.00	0.00	0.00	0.00	0.00
10	26.12 ± 0.89	15.52 ± 1.05	24.36 ± 0.89	11.10 ± 0.98	19.06 ± 0.92	17.29 ± 0.89
20	28.18 ± 0.98	20.11 ± 0.88	30.81 ± 0.88	17.41 ± 0.92	24.57 ± 1.02	20.13 ± 0.98
30	40.86 ± 0.83	29.17 ± 0.92	37.34 ± 0.92	23.79 ± 0.92	37.21 ± 0.92	35.37 ± 1.05
40	63.40 ± 1.02	34.79 ± 0.98	41.28 ± 1.02	33.77 ± 0.89	47.34 ± 1.05	45.48 ± 0.83

50	70.28 ± 0.92	44.89 ± 1.02	58.51 ± 0.89	56.23 ± 0.83	67.29 ± 0.98	60.12 ± 0.89
60	83.41 ± 0.89	72.15 ± 0.83	70.63 ± 1.05	64.79 ± 0.83	81.28 ± 0.92	71.37 ± 1.02
70	89.61 ± 1.08	85.92 ± 1.05	82.00 ± 0.92	83.17 ± 0.83	92.76 ± 1.05	90.69 ± 0.83

(Mean ±S.D., n=3).

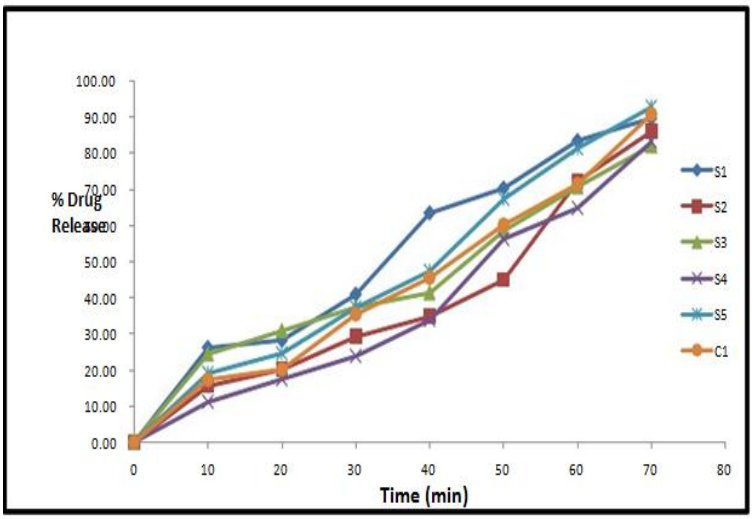

Fig. 7: In – vitro Drug Release of selegiline

Total six batches were formulated S1 - S5 and compare it with C1 batch. Among those the formulation S5 showed *In vitro* drug release 85.44% Levodopa, 92.76% Selegiline and is better than other formulation.

Stability Studies

The suppositories were wrapped in the aluminum foil and kept in stressed condition using freeze (2 - 8℃) and thaw (25℃) method. Suppositories were also kept in accelerated condition temperature (30℃) for 45 days.

Table 6: Stability Studies

Formulation Code	Parameters	2 - 8°C (6 Months)	25°C (45 Days)	30°C (45 Days)
S5	Wt. uniformity (gm)	2.2 ± 0.002	2.1 ± 0.002	2.1 ± 0.002
	Softening Time (min) at 37°C	2.5 ± 0.01	1.5 ± 0.02	1.0 ± 0.03
	Hardness Test (gm cm^2)	3.4 ± 0.02	3.0 ± 0.02	1.5 ± 0.02
	Melting Range (°C)	37 ± 0.02	37 ± 0.02	36 ± 0.02
	Drug content (%)	98.2 ± 0.03	97.8 ± 0.05	98.2 ± 0.04
	Disintegration Time (min)	5 ± 0.02	4 ± 0.02	1 ± 0.03

(Mean ±SD; n=3).

The stability studies revealed that no significant changes were seen in the physical appearance and drug content. It was found to be in the range of 99 to 100%.

DISCUSSION

Prepared suppositories were checked for morphological characters such as appearance, color and melting range. It was found that the suppositories made by using only Sal fat were soft to touch and became slippery after some time. This indicated that it may soften before reaching its melting point. Hence emulsifying wax was incorporated to increase the melting range, good mould release characteristics and impart hardness to the formulation.[1] Drug was incorporated as percentage of novel base. Tween 80 was added in the formulation to enhance drug release characteristics which may be otherwise retarded by addition of emulsifying wax. Five formulae were designed using Sal fat (S1 - S5) as novel and Cocoa butter (C) as standard suppository batch. In S1 batch emulsifying wax was not incorporated so it do not showing desirable softening time, melting range, hardness and disintegration time. Concentration of emulsifying wax was optimized at 400 mg i.e. S5 batch where the suppository shows the optimum softening time, melting range, hardness and disintegration time. Above this concentration the suppository becomes more hard. In S2 batch tween 80 was not incorporated so it do not showing desirable softening time, hardness, disintegration time and drug release.

Concentration of tween 80 was optimized at 500 mg i.e. S5 batch where the suppository shows the optimum softening time, melting range, hardness, disintegration time and drug release. Above this concentration the suppository becomes more soft and difficult to handled it.

CONCLUSION

Suppositories made by using Sal fat were soft to touch with good appearance, good mould release characteristics and off - white in colour. The results of various evaluation parameters are shown in table 11. The drug content of all the suppositories were within the permissible limits (98 - 102%) indicating the uniform dispersion of drug in Sal fat base. The hardness of Sal fat suppositories was found to be in the range of 1 - 4Kg/cm2 showing good mechanical strength for handling and transportation. The hardness of cocoa butter suppositories was found to be more than the Sal fat suppositories. The liquefaction time was found within the range of 4 - 6 min. It was found that the liquefaction time of Sal fat suppositories decreased with increase in Sal fat composition but less as compare to cocoa butter suppositories.

The *in – vitro* drug release profiles from different suppositories is shown in graph 10 .The dissolution study showed that the suppositories melted in the dissolution medium maintained at 37 ± 0.5℃. This phenomenon indicate that the Sal fat possess the important requisites of suppository base and can be used for immediate release of drugs. The drug release was also compared with cocoa butter suppositories as standard base. It was found that the drug release from formulations S1,S3,S4 and S5 showed more than 50% of drug release within 40 min. This may be due to the addition of Tween 80 in the formulation. Further the formulation S5 showed maximum release of 85.44% levodopa and 92.7 6% selegiline within 60 min of the dissolution studies. The Cocoa butter suppositories showed only 81.9% of levodopa and 91.69% selegiline release within 60 min of the drug release studies, which was somewhat less than the drug released by Sal fat suppositories which may be attributed to the lipophilicity of cocoa butter. This shows that the drug release pattern of Sal fat suppositories was comparable with Cocoa butter.

From the above studies it was found that the Sal fat suppositories had good appearance, good mechanical strength and good drug release properties. Above all it remains solid at room temperature and posses the melting temperature in the range of 30 - 36℃ which is an important prerequisite of any suppository base.

The stability studies also revealed the satisfactory results. No significant changes were seen in the physical appearance and the drug content was found to be in the range of 99 to 100%. Thus the studies suggested that Sal fat may be used as a base for conventional immediate release suppositories as it has been found that it possesses all the characteristics as possessed by ideal suppository base. It can be concluded that further there is a scope for detailed studies and evaluations for using Sal fat as cost effective excepient in preparation of suppositories and different pharmaceutical formulations.

REFRENCES

1. Larry JC, Herbert AL. Suppositories. In: Lachaman L, Lieberman HA, Kanig JC, editors. The theory and practice of industrial pharmacy. 3rd edition, Bombay: Varghese Publishing House, 1994; 564-87.
2. Wani TA, Kumar D, Prasad R, Verma PK, Sardar KK, et al, Analgesic activity of the ethanolic extract of Shorea robusta resin in experimental animals, Indian J Pharmacol. 2012 Jul - Aug; 44(4): 493 – 499.

3. Srihari R, Adamkhan P, Reddy PS, Sasikanth K, Brahmaiah B, An Emerging Trend on Bilayer Tablets, International Journal of Innovative Drug Discovery, 2013; 3(21): 45-50.
4. Bio Chemica International, 875 Creel Street - Melbourne, FL 32935 USA E – mail: techhelp@biochemica.com, Web Site: http://www.biochemica.com.
5. M. Baker, O. S. Gershanik, Parkinson's Disease, Neurological Disorders Public Health Challenges, World Health Organization, 2006; 140.
6. Rang HP, Dale MM, Ritter JM, Flower RJ, Rang and Dale's Pharmacology, Elsevier Churchill Livingstone, 2012; 7: 485-487.
7. Tripathi KD, Essentials of Medical Pharmacology, Jaypee Brothers Medical Publishers (P) Ltd, 2013; 7: 425-426.
8. Mohit ST, Ashish Kumar K, Shikha AD and Dishant G. Bi - Layer Tablets: An Emerging Trend, International Journal of Pharmaceutical & Biological Archives, 2012; 3(3): 499-506.
9. Tengale NB, preparation and evaluation of rectal suppositories of primaquine M.pharm dissertation protocol submitted to the Rajiv Gandhi University of health sciences, Bangalore, Karnataka.
10. Swamy PV, Ali M Y, Kumar YA, Prasad K, Srinivaslu N, Design and evaluation of rectal drug delivery systems of nonsteroidal anti - inflammatory drug. International Current Pharmaceutical Journal, 2012; 1(7): 165–170.
11. Reddy AU, Sreeramulu J, Punna S, Formulation and Development of Losatan Potassium Microsphere Using Natural Polysacharides and their In – Vitro Evaluation, Research Journal of Pharmaceutical Biology and Chemical Sciences, 2012; 3(2): 725-734.
12. Prasanna L, Deepthi B., Rao R N, Review article. Rectal drug delivery: A promising route for enhancing drug absorption, Asian Journal of Pharmaceutical Sciences. 2012; 2(4): 143-149.
13. Matsuda H, Arima H. Cyclodextrins in transdermal and rectal delivery. Advanced Drug Delivery Reviews., 1999; 36: 81–99.
14. Aulton ME. Pharmaceutics the science of dosage forms design. Churchill Livingstone. 2002; 2nd ed; 534-537.
15. Sari D. Cooper, Hala A, Ismail, Christopher Frank. Case report: Successful use of rectally administered levodopa – carbidopa.