Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2016, 8 (6):87-101
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Formulation and development of mucoadhesive tablets of rebamipide by using design of experiment

Ganesh Kumar Gudas*[1], A. Jaswanth[2] and D. V. R. N. Bhikshapathi[3]

[1]*Srikrupa Institute of Pharmaceutical Sciences, Siddipet*
[2]*Procadance Institute of Pharmaceutical Sciences, Gajwel*
[3]*CMR College of Pharmacy, Kandlakoya, Hyderabad-501401, Telangana, India*

ABSTRACT

The aim of the present work was to prepare and evaluate mucoadhesive tablets of Rebapimide to prolong the gastric residence time after oral administration. The solubility of Rebapimide was enhanced by kneading technique with that mixture formulations were prepared by using 3^3 full factorial designs to explore the effects of Gum Kondagogu, Gum Olibanum and Guar Gum (as independent variables) on mucoadhesive strength, drug release and Ex vivo residence time (as dependent variables). The tablets were evaluated for various parameters such as compatibility studies, drug content, weight variation, hardness, thickness, friability, swelling studies, in vitro drug release studies, in vitro mucoadhesion strength , Ex vivo residence time test and release rate kinetics. The drug-polymer interaction was also studied by conducting FTIR. The in vitro release kinetics studies reveal that all formulations fits well with Zero order, followed by Korsmeyer-Peppas, Higuchi and the mechanism of drug release is erosion. After analysis of different evaluation parameters and drug release kinetics, formulation code F13 was selected as a promising formulation for delivery of Rebapimide as a mucoadhesive Gastroretentive tablet with best mucoadhesive strength and 99.34% drug release at 12^{th} hour. The main effects and the interaction terms were quantitatively evaluated by quadratic model. The stability studies were carried out at 40°C/75% RH for 180 days. There was no significant change in the physical property and weight variation, hardness, thickness, friability, in vitro drug release studies, in vitro mucoadhesion strength, drug content during the study period.

Keywords: Rebamipide, Gastro-retentive tablet, Mucoadhesive tablets, Mucoadhesive strength.

INTRODUCTION

Gastro retention is also used for achieving local delivery of drug to the stomach and proximal small intestine [4]. Gastro retentive formulations could be designed based on approaches like: (a) floating; (b) high density system; (c) bioadhesion; (d) lowered motility of the GIT by concomitant administration of drugs or pharmaceutical excipients ; (e) swellable and expandable systems. In the current study we have targeted at bioadhesion to the stomach mucosa [1].

Naturally occurring polymers, being biocompatible and biodegradable, are currently extensively researched for the development of novel drug delivery systems. There are number of drugs like domperidone, ranitidne, theophylline those have narrow absorption window from upper GIT i.e. stomach. Due to short gastric resident time less than 3 hr these drug reaches the non absorbing distal parts of intestine. Therefore main challenge is to prolong the resident time of drug in stomach. Gastro retentive drug delivery techniques are primarily controlled release drug delivery

systems, which gets retained in the stomach for longer period of time, thus helping in absorption of drug for the intended duration of time [2].

Rebapimide,(±)-2-(furfurylsulfinyl)-N-(4-[4-[piperidinomethyl]-2-pyridyl]oxy-(Z)-2-butenyl) acetamide is a newly developed 2 nd generation histamine H2-receptor antagonist. It is used in the treatment of gastric ulcers, duodenal ulcers, and gastric mucosal lesions associated with acute gastritis and acute exacerbation of chronic gastritis. It is absorbed in the small intestine, reaches gastric cells via the systemic circulation, and rapidly binds to gastric cell histamine H2 receptors, resulting in immediate inhibition of gastric acid secretion.

MATERIALS AND METHODS

Materials:
The Rebapimide was obtained as a gift sample from splendid laboratories, Pune. Gum Kondagogu, Gum Olibanum and Guar Gum were obtained from Girijan Co-operative corp. Ltd, Hyderabad. PVP-K30 was gifted from MSN Labs Ltd, Hyderabad. All other chemicals used were of analytical grade.

Preparation of PEG 4000- Rebapimide
Solid Dispersion
a) Preparation by kneading method
The required amount of Rebapimide and carrier in 1:1, 1:2 & 1:3 ratio were wetted with sufficient volume of methanol and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed was dried under vacuum for 24 hours. Dried powder was passed through sieve no. 60 and stored in desiccators until further evaluation [6].

Formulation prepared by kneading method using Rebapimide and PEG 4000 of ratio 1:2 (F8) yielded best results in terms of dissolution rate.

PREPARATION OF MUCOADHESIVE TABLETS
WET GRANULATION METHOD:
Mucoadhesive tablets of Rebapimide were prepared by wet granulation technique using different concentrations of Gum Kondagagu, Gum olibanum and Guar gum. All the ingredients were passed through sieve no 85# and were mixed uniformly. Granulation was carried out with sufficient quantity of binder solution (PVP K 30 - 5% in isopropyl alcohol). Wet mass was passed through sieve no 12# and dried at 45-55 ^{0}C for 1 hr. Dried granules were sized by sieve no.18# and add magnesium stearate and talc. Granules obtained were compressed with 9 mm flat punch (Cadmach, Ahmedabad, India) [3].

The formulations are made by using design of experiment method (factorial designs)
Study type: **Response Surface**
Design type: **Central Composite**
Design mode: **Quadratic**

Table No: 1 Design Summary of Formulation by Natural Polymers

F.NO	REBAMIPIDE (mg)	GK (mg)	GO (mg)	GG (mg)	MCC (mg)	PVP K-30 (mg)	TALC (mg)	MAGNESIUM STEARATE (mg)	TOTAL WEIGHT (mg)
F1	200	15	15	30	122	12	3	3	**400**
F2	200	45	15	30	117	12	3	3	**400**
F3	200	15	45	30	117	12	3	3	**400**
F4	200	45	45	30	72	12	3	3	**400**
F5	200	15	30	30	139	12	3	3	**400**
F6	200	45	30	30	94	12	3	3	**400**
F7	200	30	15	30	139	12	3	3	**400**
F8	200	30	45	30	94	12	3	3	**400**
F9	200	30	30	30	116	12	3	3	**400**
F10	200	15	15	60	132	12	3	3	**400**
F11	200	45	15	60	87	12	3	3	**400**
F12	200	15	45	60	87	12	3	3	**400**
F13	200	45	45	60	42	12	3	3	**400**
F14	200	15	30	60	109	12	3	3	**400**
F15	200	45	30	60	64	12	3	3	**400**
F16	200	30	15	60	109	12	3	3	**400**
F17	200	30	45	60	64	12	3	3	**400**
F18	200	30	30	60	86	12	3	3	**400**
F19	200	15	15	90	87	12	3	3	**400**
F20	200	45	15	90	42	12	3	3	**400**
F21	200	15	45	90	42	12	3	3	**400**
F22	200	45	45	90	03	12	3	3	**400**
F23	200	15	30	90	64	12	3	3	**400**
F24	200	45	30	90	19	12	3	3	**400**
F25	200	30	15	90	64	12	3	3	**400**
F26	200	30	45	90	19	12	3	3	**400**
F27	200	30	30	90	41	12	3	3	**400**

GK: GUM KONDAGOGU GO: GUM OLIBANUM GG: GUAR GUM.
MCC: MICROCRYSTALLINE CELLULOSE PVP K-30: POLYVINYL PYROLIDONE K-30

Evaluation of Rebapimide mucoadhesive Tablets

Thickness

The thickness of the prepared tablets was tested using vernier calipers. The test was done in triplicate and average thickness was determined [4].

Hardness

Hardness of prepared tablets was determined using Monsanto hardness tester and measured in terms of kg/cm^2 [4].

Weight variation

Formulated tablets were tested for weight uniformity. Twenty randomly taken tablets were weighed together and the average weight was determined. Each tablet was then weighed individually and deviation from average weight was calculated. The percent weight variation was calculated by using the following formula [4].

$$\% \text{ Weight variation} = \frac{\text{Average weight - Individual weight}}{\text{Average weight}}$$

Friability

The Roche friability test apparatus (Electrolab) was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus operated for 4 min at a speed of 25 rpm. The tablets were removed from the friabilator, de-dusted and reweighed. The percentage friability was calculated according to the following formula [4].

$$\%\text{Friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

Content Uniformity:
20 tablets were randomly selected and average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 10 mg was weighed and dissolved in 100ml of 1.2 pH 0.1 N HCl filtered and drug content analyzed spectrophotometrically in UV spectrophotometer at 227 nm [4].

***In Vitro* Swelling Studies:**
The degree of swelling of mucoadhesive polymer is an important factor affecting adhesion. For conducting the study, a tablet was weighed and placed in a petri dish containing 5 ml of 0.1 N HCl buffer pH 1.2 in 6 h at regular intervals of time (1, 2, 4, and 6h), the tablet was taken carefully by using filter paper. The swelling index was calculated using the following formula [4].

$$\text{Swelling Index (S.I)} = (Wt-Wo)/Wo\times100$$

Where S.I = swelling index, Wt = weight of tablet after swollen at time t Wo= weight of the initial tablet.

Microenvironment pH:
The microenvironment pH (surface pH) of the Mucoadhesive tablets was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. The method adopted by Battenberg *et al* was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 5 mL of distilled water (pH 6.5 ± 0.05) for 2 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablets and allowing it to equilibrate for 1 min [4].

***In-vitro* dissolution studies:**
The USP dissolution test apparatus (apparatus II paddle type) was used to study the drug release from the tablets. The dissolution medium was 900 ml of 0.1N HCl buffer pH 1.2. The release was performed at 37 ± 0.5°C, with a rotation speed of 100 rpm. 5ml samples were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through whatmann filter paper and analyzed after appropriate dilution by UV spectrophotometer at 227 nm and drug release was determined from standard curve [4].

Dissolution Parameters:
Dissolution medium: 900 ml of 0.1 N HCl buffer with pH 1.2
RPM: 100
Temp: 37 ± 0.5°c
Sample volume withdrawn: 5ml sample
λ *max* : 227 nm
Time interval: 0, 1, 2, 3, 4, 6, 8, 10 & 12h.

***Ex-Vivo* Residence Time Test:**
The disintegration test apparatus is used for the study of Ex-vivo residence time of tablets. The intestinal mucosa is collected and is cut in to 2×2 size pieces. These pieces are placed on the glass sides and tied with rubber bands. The formulations are placed on the tissue and kept aside for few minutes. Then all glass slides are fitted to the disintegration test apparatus and the apparatus is allowed to start this process is continued for 12 hours. The residence time of of each formulation is noted as *Ex-vivo* residence time [4].

Mucoadhesive Strength:
Mucoadhesive strength was determined by using modified physical balance method, for which Goat stomach mucosa was collected from local slaughter house and stored in Krebs solution. Mucosa was sticked on glass slide using double sided sticker which was already sticked on the bottom of 100 ml beaker, and this beaker was placed in 1Ltr beaker which already contained 0.1N HCl of pH 1.2. Tablet were sticked on lower side of left pan of double pan balance using double sided sticker, in both pan of the balance empty beaker were placed and their weight were adjusted, near to the right sided pan arrangement of burette were made for drop wise addition of water, as shown in figure . The mucosal and tablet surface was wetted with few drop of 0.1N HCl and on the left pan tablet 5 gm weight was placed for 5min. to allow the initial contact of mucoadhesion. Then drop wise water was added in beaker of

right pan till the detachment of tablet from the mucous membrane was observed. Then weight of water present in right pan beaker was determined, using following formula [4].

Mucoadhesive strength = (Wt.of the beaker + Wt. of the water) – Wt. of the empty beaker.

After determination of mucoadhesive strength Force of adhesion was calculated using formula

A: Burette B: Beaker for collection of water
C: Wt. adjustment for pan D: 1 lit. Beaker having dissolution medium
E: Glass slide along with mucous F: Modified physical double pan balance
G: focus showing adherence of tablet to mucous membrane

Force of adhesion (N) =Mucoadhesive strength / 100×9.81

RESULTS AND DISCUSSION

Physico-chemical parameters of Rebamipide mucoadhesive tablets

The prepared tablets were evaluated for different physico-chemical properties and the results are found to be within the pharmacopoeial limits, which depicted in Table No 2 & 3.

Table: 2 Physico-Chemical Parameters of Rebamipide Mucoadhesive Tablets

Formulation	Swelling index (%)	Surface p^H	Mucoadhesive strength(g)	Residence time (hrs)
F1	71	6	05.34	2
F2	77	5.7	10.23	3
F3	76	6.1	11.42	3
F4	86	6.2	15.39	8
F5	71	5.7	09.45	3
F6	70	5.8	13.24	7
F7	68	5.7	09.78	3
F8	80	6	12.34	8
F9	79	6	12.23	6
F10	75	5.8	11.45	6
F11	84	6.1	17.78	8
F12	86	6.2	18.14	8
F13	**98**	**6.1**	**26.84**	**12**
F14	81	5.8	15.78	9
F15	89	5.9	21.16	9
F16	86	5.7	17.39	8
F17	92	6.2	20.11	10
F18	94	6.3	25.29	10
F19	89	5.7	20.11	8
F20	88	5.7	23.59	9
F21	90	6	23.67	9
F22	95	6.3	24.12	11
F23	86	6	23.12	9
F24	96	6.2	24.78	11
F25	93	6.1	21.16	9
F26	97	6.2	24.28	11
F27	98	6.3	25.33	11

Table: 3 Physico-chemical parameters of Rebamipide mucoadhesive tablets:

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity (%)
F1	400±2.25	5.1±0.15	5.3±0.69	0.53±0.26	97.23±0.82
F2	399±2.56	5±0.38	5±0.36	0.54±0.48	98.04±0.48
F3	398±1.89	5.1±0.91	5.3±0.45	0.63±0.17	96.56±0.39
F4	401±01.25	5.2±0.27	5.2±0.36	0.56±0.67	99.11±0.85
F5	402±2.45	5.1±0.64	5.1±0.82	0.61±0.22	95.23±0.23
F6	400±1.85	5.2±0.22	5.2±0.51	0.67±0.14	96.45±0.58
F7	400±1.78	5±0.19	5±0.55	0.54±0.57	95.11±1.05
F8	399±1.55	5.2±0.45	5.2±0.45	0.67±0.89	98.23±1.65
F9	400±2.71	5.2±0.15	5.2±0.64	0.56±0.45	97.13±1.45
F10	403±1.68	5.1±0.42	5.1±0.27	0.77±0.23	96.23±0.75
F11	401±2.35	5.1±0.38	4.9±0.78	0.76±0.27	98.77±0.39
F12	402±1.65	5.4±0.69	4.6±0.19	0.73±0.86	98.45±1.59
F13	**400±2.15**	**5.5**±0.25	**5.1**±0.44	**0.72**±0.56	**99.95**±0.95
F14	398±2.56	5.1±0.13	5.2±0.21	0.72±0.29	99.38±0.65
F15	399±1.61	5.5±0.78	5.6±0.55	0.71±0.37	99.45±1.56
F16	400±155	5.1±0.62	5.2±0.67	0.78±0.16	97.45±0.78
F17	401±2.41	5.5±0.51	4.7±0.39	0.79±0.35	99.34±0.29
F18	401±0.95	5.5±0.92	4.6±0.28	0.82±0.48	99.56±1.85
F19	399±2.69	5±0.98	5±0.49	0.84±0.99	99.29±0.27
F20	399±1.27	5.3±0.65	5.5±0.75	0.63±0.29	97.18±0.65
F21	398±2.34	5.2±0.43	5.3±0.33	0.66±0.65	96.27±1.45
F22	401±1.65	5±0.82	5.1±0.79	0.72±0.35	98.34±0.15
F23	400±1.54	5.3±0.45	4.8±0.13	0.76±0.27	99.14±0.75
F24	400±1.35	5.4±0.36	4.9±0.48	0.73±0.39	98.16±1.55
F25	399±1.89	5.1±0.22	4.6±0.15	0.67±0.38	98.23±0.85
F26	400±2.43	5.3±0.94	5.7±0.66	0.72±0.77	99.34±1.25
F27	400±1.67	5.5±0.64	4.9±0.27	0.89±0.68	98.10±0.96

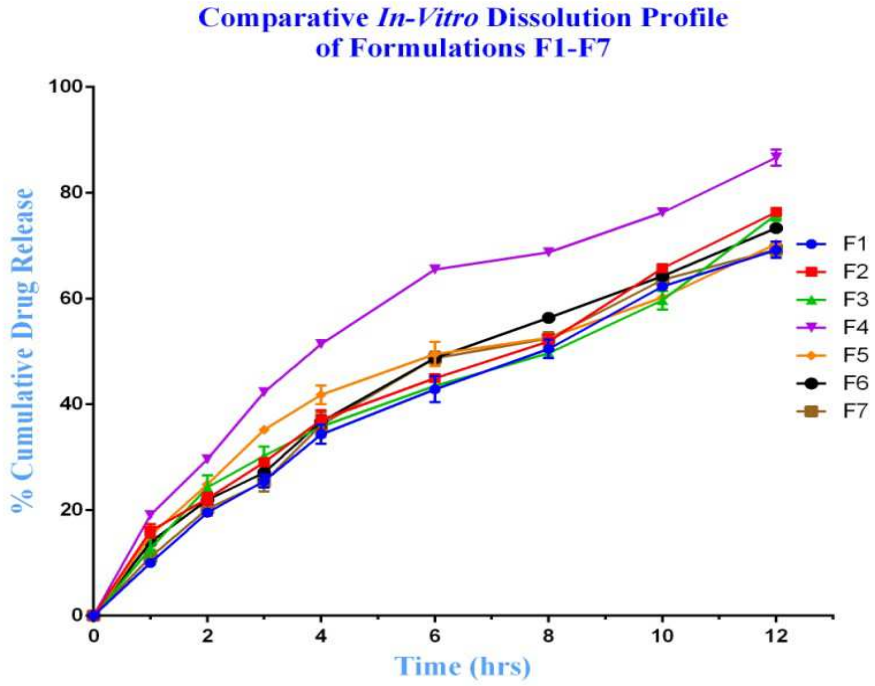


Fig:2 Percentage Drug Release of Rebapimide F1-F7

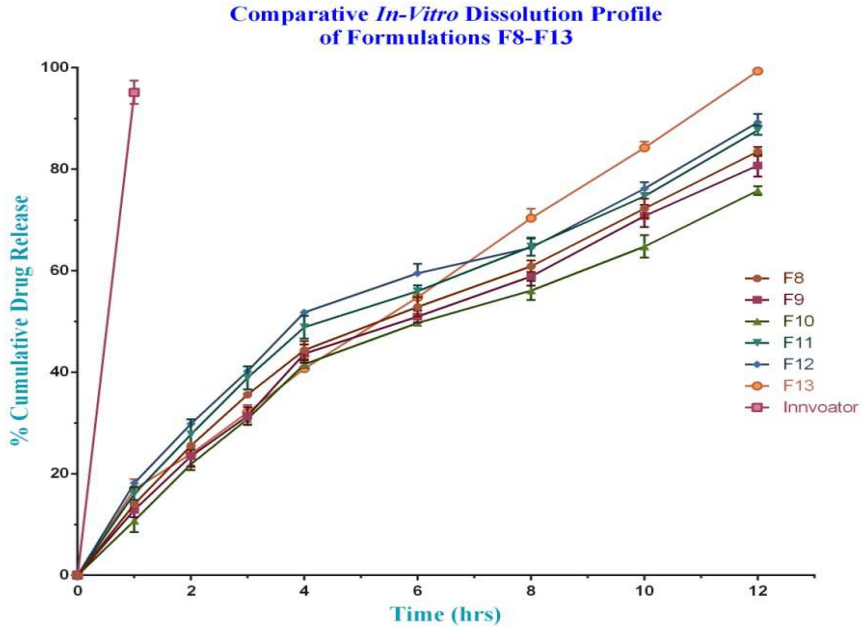


Fig: 3 Percentage Drug Release of Rebapimide F8-F13

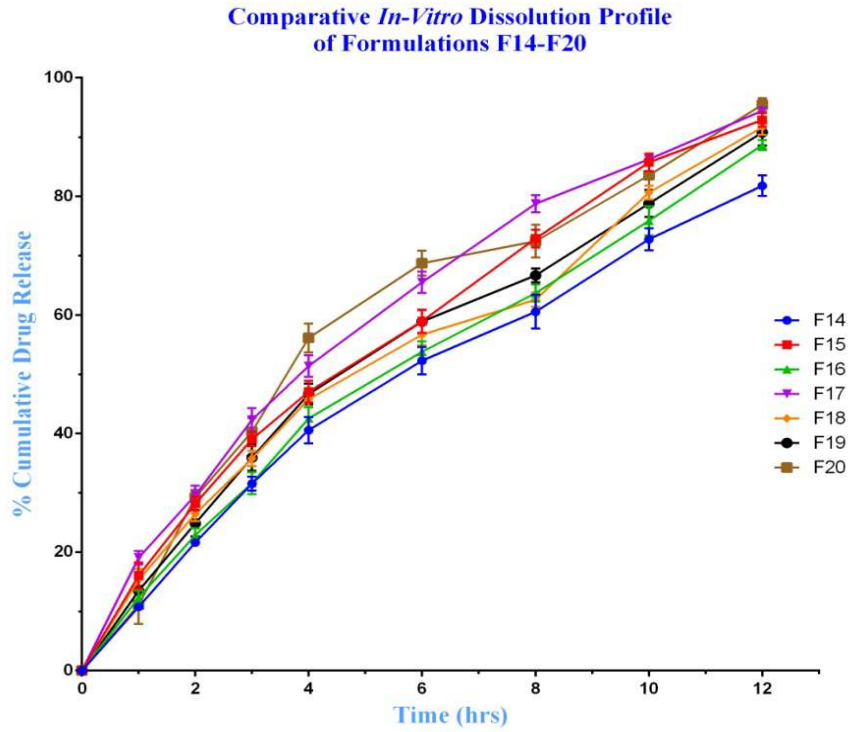


Fig: 4 Percentage Drug Release of Rebapimide F14-F20

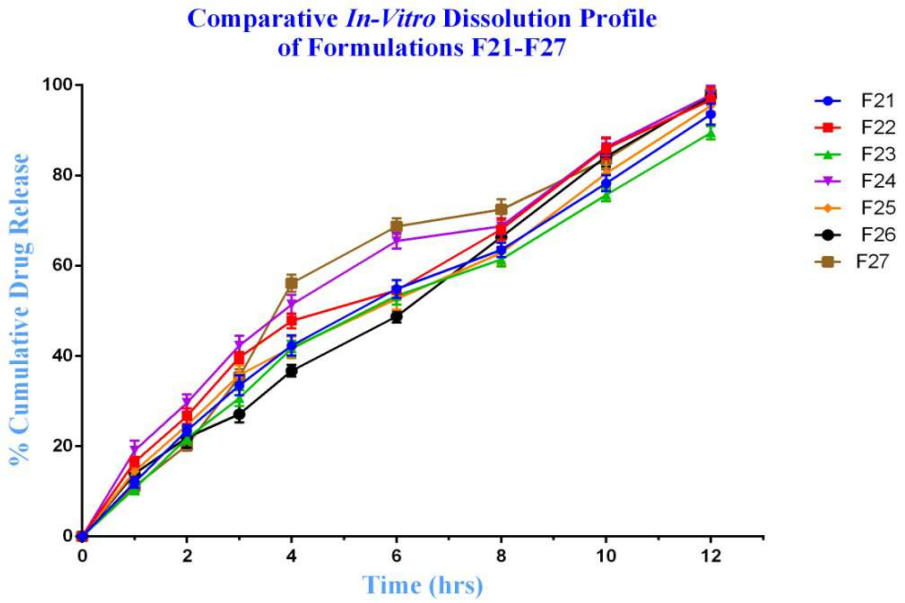


Fig: 5 Percentage Drug Release of Rebapimide F21-F27

Fig : 6 Goat mucous membrane

Fig : 7 Optimized Rebapimide mucoadhesive tablet on

Fig: 10 *Ex-Vivo* Mucoadhesion test of Rebapimide mucoadhesive tablet

Fig:11 *Ex-Vivo* Mucoadhesion test of Rebapimide mucoadhesive tablet

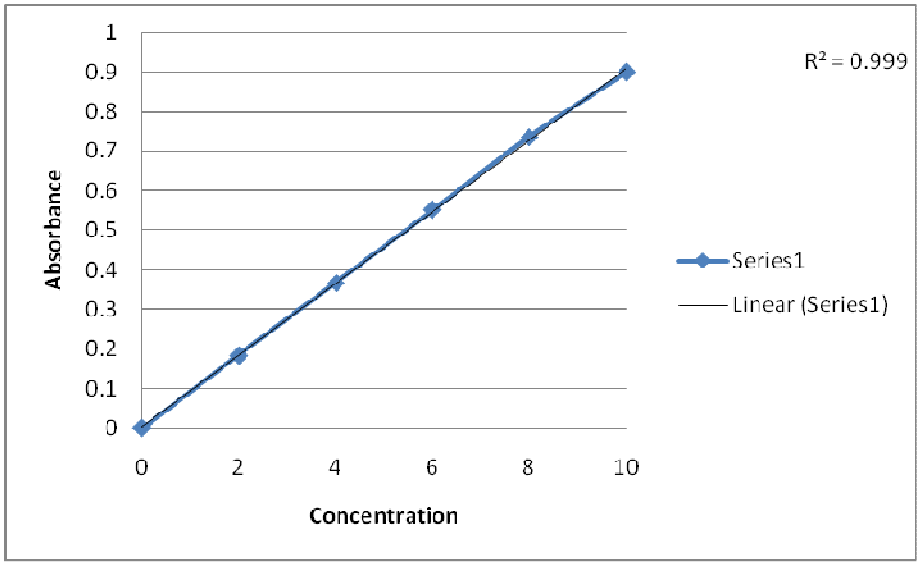


Fig: 12 Standard graph of Rebamipide

Drug excipient compatibility studies
FTIR Studies

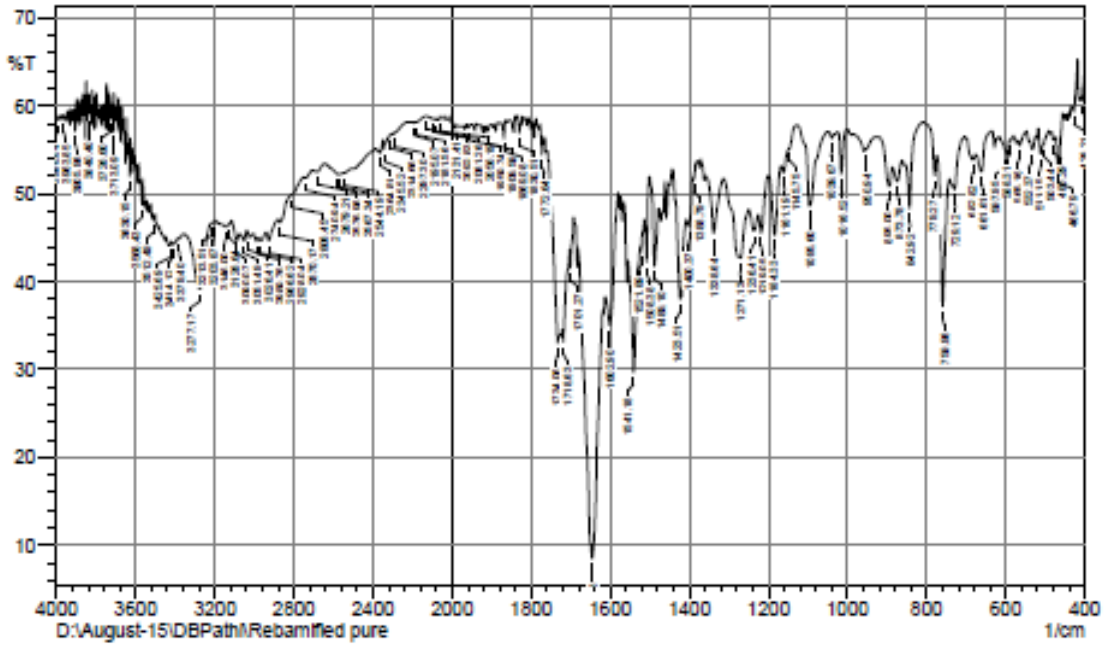


Fig: 13 FT-IR spectrum of pure drug Rebamipide

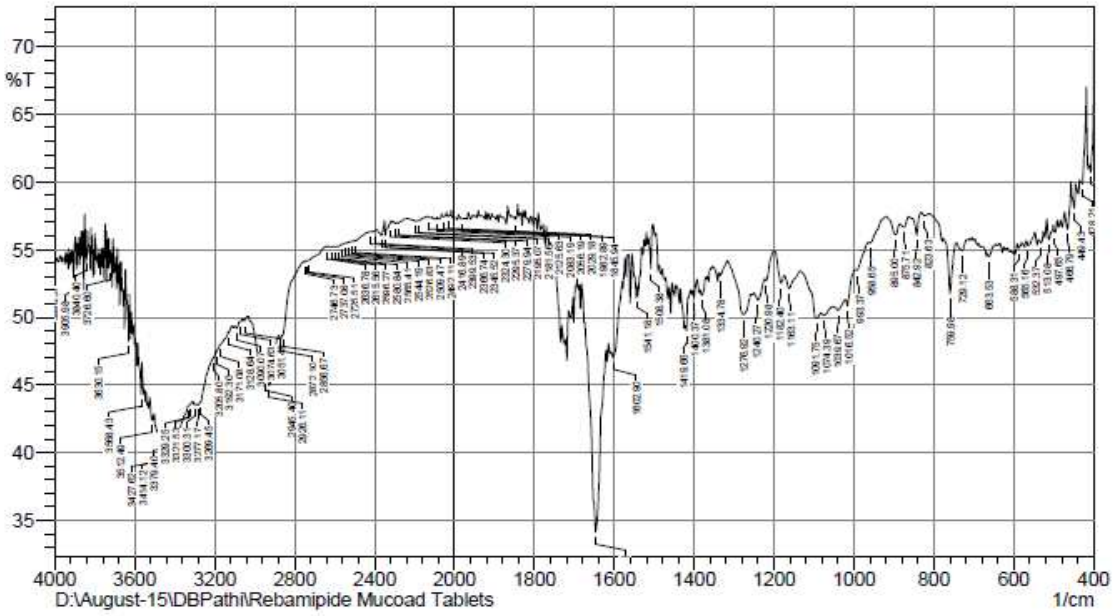


Fig : 14 FTIR spectrum of optimized Rebamipide formulation F13

Table: 4 Release kinetics of optimized formulation of Rebamipide mucoadhesive tablets

Formulation Code	Zero Order		First Order		Higuchi		Korsmeyer-Peppas	
	R^2	K	R^2	K	R^2	K	R^2	N
F13	0.993	7.873	0.766	0.131	0.953	29.08	0.554	2.175

From the above results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e.0.993 indicates that the drug release follows a zero order mechanism (Table no). This data indicates a lesser amount of linearity when plotted by the first order equation. Hence it can be concluded that the major mechanism of drug release follows zero order kinetics.

Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modeling such as Higuchi and Korsmeyer-Peppas plots. The mass transfer with respect to square root of the time has been plotted, revealed a linear graph with regression value close to one i.e. 0.953 starting that the release from the matrix was through diffusion. Further the n value obtained from the Korsmeyer-Peppas plots i.e. 0.554 suggest that the drug release from tablets was anomalous Non fickian diffusion.

Design of experiments

This method is mainly used to explain the effect of one factor on other factor. Whether this effect is significant or not. If significant how it influence the response. In this present work the effect of one factor (Guar Gum) on other two factors (Gum Kondagogu, Gum Olibanum) is explained.

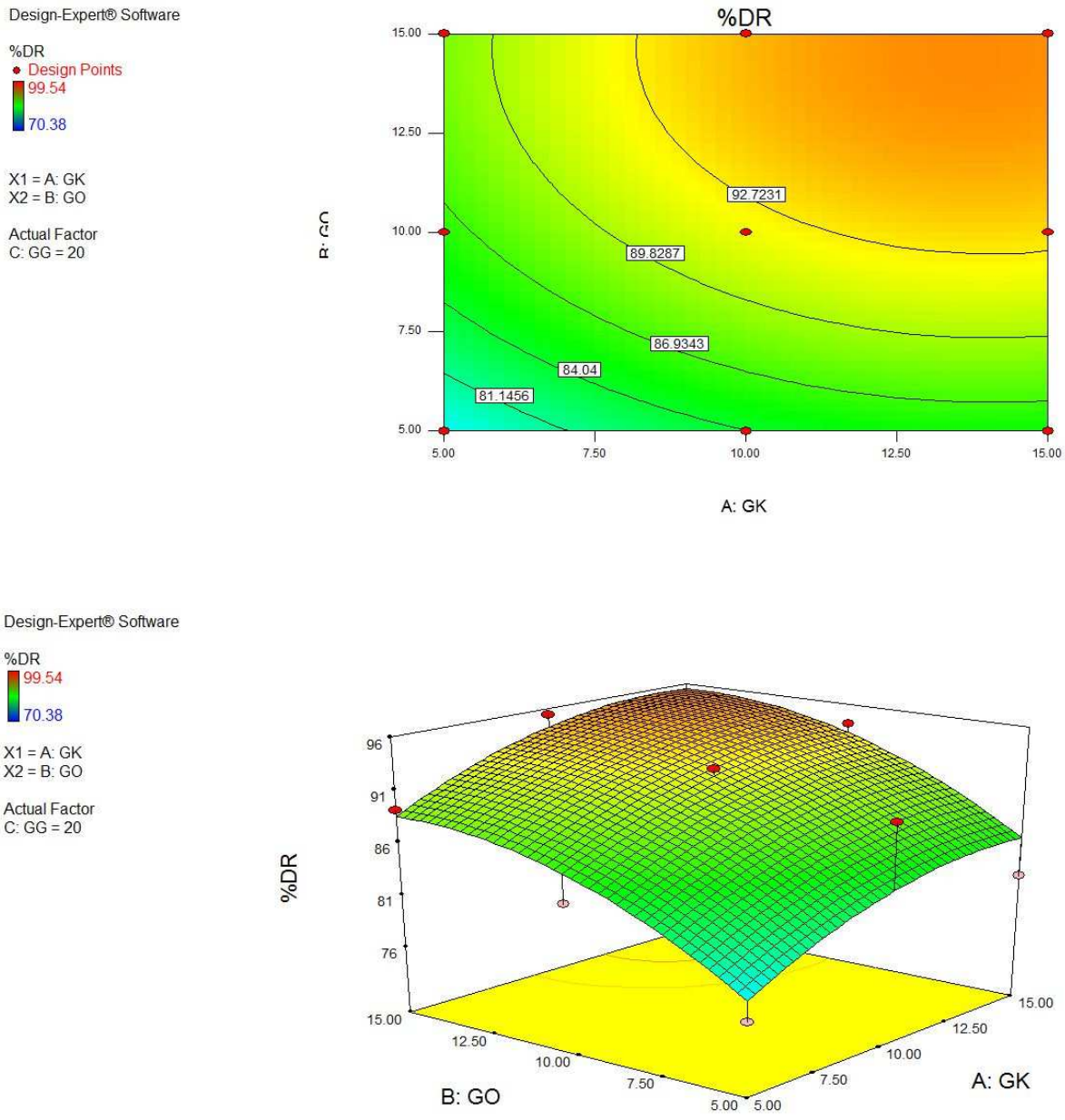


Fig: 15 Response surface plot for %CDR

In the above graph the effect of Guar Gum on % cumulative drug release is examined and it clearly indicates that there is a very significant effect of Guar Gum on % cumulative drug release. The formulations with all 3 factors shown % drug release in between

70.38-99.54. but when Guar Gum is removed from the formulations the maximum % CDR is near 70. This is the effect of factor (Guar Gum**)** on response

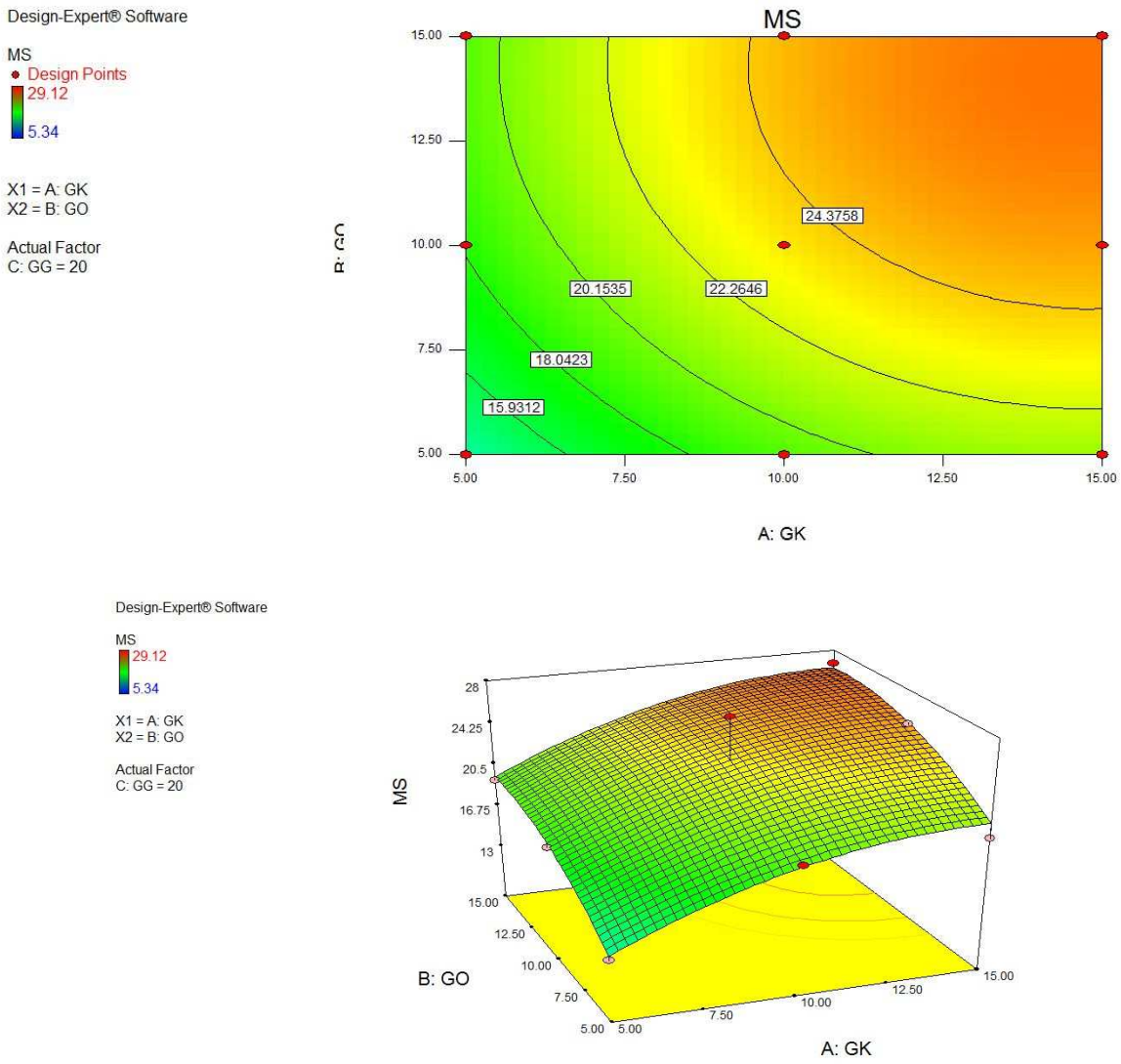
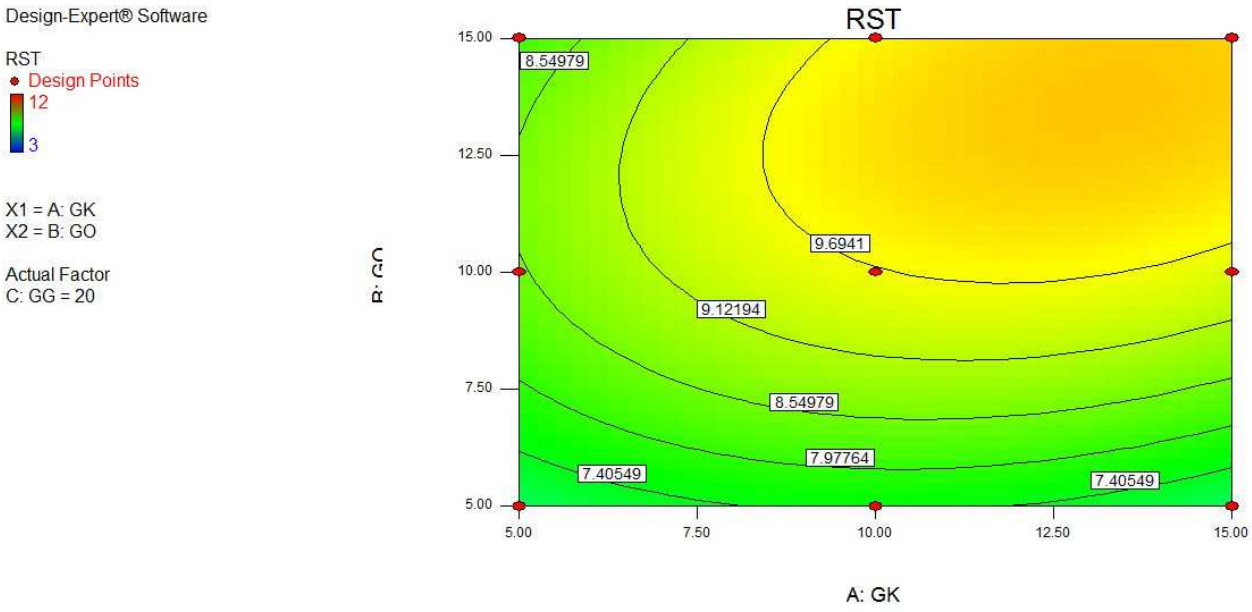


Fig : 16 Response surface plot for mucoadhesive strength

There is a negligible effect on mucodhesive strength of formulations because all formulations have excellent mucoadhesive property and there is slightly influence on mucoadhesive strength by Guar Gum.



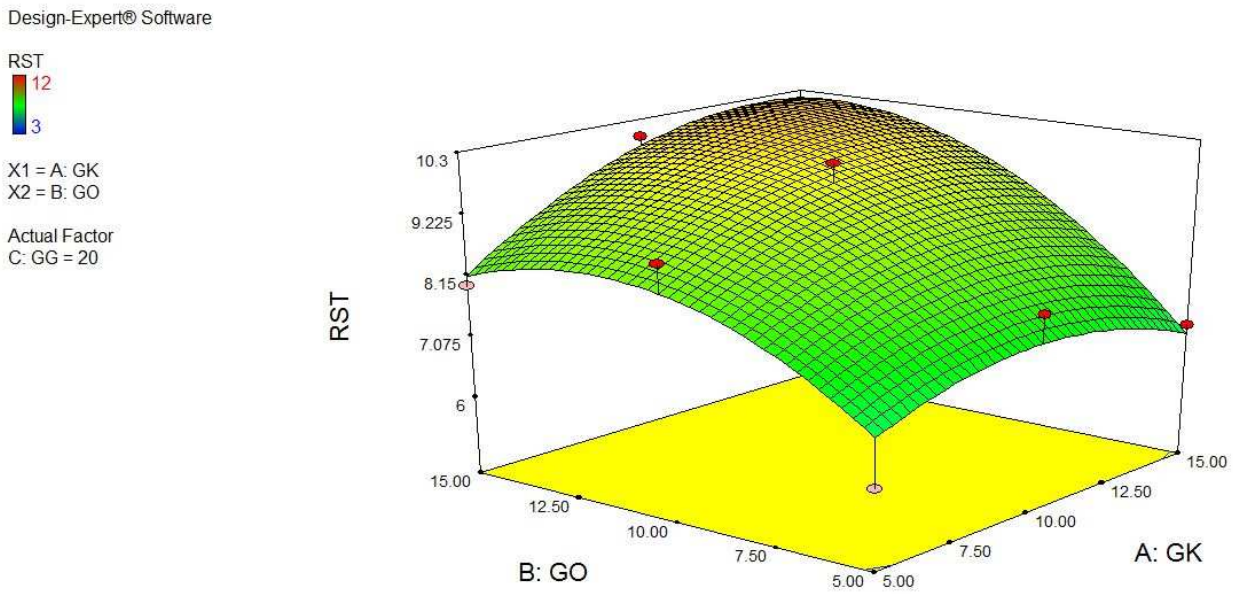


Fig: 17 Response surface plot for *Ex vivo* residence time

There is a small effect of Guar Gum on *Ex vivo* residence time of formulations. The formulations without Guar Gum have shown maximum *Ex vivo* residence time is nearly 10 hours.

CONCLUSION

Rebamipide mucoadhesive oral tablets could be formulated using the drug, Gum Kondagogu, Gum Olibanum and Guar Gum with different proportions using 3^3 full factorial designs. It can be seen that there is a synergistic effect when polymers are used in combinations. There is a significant effect of Guar Gum in formulations on drug release rate from the tablets and mucoadhesive strength was also increased. The *in vitro* release kinetics studies reveal that all formulations fits well with Zero order, followed by Korsmeyer-Peppas, Higuchi and the mechanism of drug release is erosion. From the formulations F1-F27 the formulation F13 was selected as optimized formulation because it showed maximum release and the other properties such as swelling index was also low, mucoadhesion force shown good and the Post and pre compression parameters were found to be within the Pharmacopeial limits.

REFERENCES

[1]Chavanpatil MD, Jain P, Chaudhari S, Shear R, Vavi PR. *Int J Pharm*. **2006**; 316(1): 86–92.
[2]Park, K. Robinson, J.R. *Int J Pharm*. **1984**; 19(2): 107–127.
[3]Shinde A J. Gastro retentive Drug Delivery System: AnOverview.Pharmainfo.net.**2008**: 6(1):182. ; Hwang S J. Park H. and Park K..Gastric Retentive Drug-Delivery Systems Critical Reviews in Therapeutic Drug Carrier Systems.**1998**:15(3):243–284.
[4]Whitehead L. Fell J T and Collett J H. *Eur. J. [8]. Pharm .Sci*. **1996**:4 (1):182.
[5]Xiaoling L. and Bhaskara R J. Design of controlled release drug delivery systems. Mc Graw Hill,New York. **2006**: 173-176.
[6]Mahaparale PR, Gudsoorkar VR, Gajeli GB and Kuchekar BS. *Ind. J. Pharm. Educ. Res*. **2006**; 40(4): 241-244.
[7]Deshpande A. A.Rhodes C T. Shah N H and Malick A W. *Drug Dev Ind. Pharm*.**1996**:22 (6):531-539.
[8]Bardonnet P L. Faivre V. Punj W J. Piffaretti J C.and Falson F. *Journal Control Release*. **2006**:111, 1-18.
[9]Bernkop A. *Adv Drug Deliv Rev*.**2005**: 57, 1553– 1555.
[10]Thripathi KD, Essentials of medical pharmacology, 6th edition: 489- 90.
[11]Sweetman SC. Ed Martindale: The complete drug reference. 35th Edition Pharmaceutical Press: London **2007**; 1250- 1253.
[12]Raymond J, Rowe C, Paul J Sheskey, sian c owen, editors. Handbook of pharmaceutical excipients 5th ed. London: Pharmaceutical Press; **2009**: 118-121, 110-114, 185-188, 94-98.
[13]Prasanna Kumari J, Ramarao T, Jayaveera K N, Bhikshapathi D V R N, Madhusudan Rao Y. *International Journal of Drug Delivery* 6 (**2014**) 14-23.
[14]Shinkar et al. *Int J Pharm Pharm Sci*, Vol 3, Issue 3, **2011**, 159-164
[15]Yu Guo, Yongjun Wang, Lu Xu *Asian Journal of Pharmaceutical Sciences* Volume 10 Issue 3, *June* **2015**, *Pages 223–229*