How to Cite:
Patil, C. C., Jorapur, P., & Naikwadi, A. (2022). Formulation and evaluation of colon targeted extended-release prednisolonematrix tablets. *International Journal of Health Sciences*, *6*(S5), 10734–10746. https://doi.org/10.53730/ijhs.v6nS5.10871

Formulation and evaluation of colon targeted extended-release prednisolonematrix tablets

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***Abstract*---**The prepared tablets met the compendia limits in termsof physiochemical parameters and dissolution studies. The mixture of 30 mg pectin and 30 mg of xanthan gum as matrix and 10% w/v of Eudragit RS100 solution as coating material were best suitable in colon targeted drug delivery system to provide optimum prednisolone release and protect it from SGF and SIF. As a result, colon delivery of prednisolone appeared to be apromising alternative to its traditional oral formulation.

***Keywords*---** prednisolonematrix, Chemicals, traditional oral formulation.

Introduction

Ease of administration, high patient compliance, low sterility limitations and flexibility in dosage form design made oral dosage formas most convenient and widely used mode of drug delivery (Dangiet al., 2013; Dhadde et al., 2020).When a traditional tablet dosage form is taken orally, it dissolves in the stomach or intestinal fluid and drug absorbed there(Dhadde et al., 2020). It is a significant disadvantage of traditional oral dose form in situations when medications must be delivered locally in the colon or where a drug must be protected from the hostile environment of the upper gastrointestinal tract (Hadiet al, 2016; Dhadde et al., 2020).

Oral delivery of drugs to the colon is critical in the treatment of colon diseases (ulcerative colitis, Crohn's disease, carcinomas and infections such as helminthiasis) because it allows for high local concentration while minimizing side effects caused by drug release in the upper GIT or unnecessary systemic absorption (Dangiet al., 2013; Hadiet al, 2016).A variety of approaches are being used to target medications, particularly to the colon.CoatingwithpH-dependentpolymers,designingtimed-releasedosageforms byutilization of redox-sensitive polymer andmicrobially triggered drug release are the methodsfordirectingorallydeliveredmedicationstothecolon (Chickpetty et al., 2010; Dangiet al., 2013; Hadiet al, 2016).Microbially triggered drug release is an enzyme-dependent method in which carriers or polymers are destroyed by colonic bacteria-produced enzymes(Mohapatra et al., 2011, Dangiet al., 2013; Hadiet al, 2016).Azoreductase, arabinosidase, glucuronidase, galactomannase, galactosidase, nitroreductase, xylosidase, deaminase, and ureadehydroxylaseare among the enzymes produced by the microflora(Mohapatra et al., 2011, Dangiet al., 2013; Hadiet al, 2016).These enzymes are mostly found in the colon, henceresearchers are exploring manyenzyme degradable polymers as carriers for colon-targeted drugs. Pectin, chondroitin sulphate, amylase, guar gum, xanthan gum and chitosan are the examples of the polymers investigated for colon-specific drug delivery(Mohapatra et al., 2011, Dangiet al., 2013; Hadiet al, 2016). Prednisolone is acorticosteroiddrug with predominantglucocorticoidand lowmineralocorticoidactivity, useful in treating a wide spectrum of inflammatory andautoimmunediseases including rheumatoid arthritis, ulcerative colitis and Crohn's disease (Fiel et al., 2006; Liu et al., 2013).

Rheumatoid arthritis (RA) is a chronic inflammatory disease that destroys the integrity of joints (Lin et al., 2020; Puentes-Osorio et al., 2021).Joint pain and functional impairment symptoms are common in people with this disease, and they are most noticeable in the early morning hours (Hadiet al, 2016; Lin et al., 2020; Puentes-Osorio et al., 2021).The notion of chronotherapy can be utilized to improve rheumatoid arthritis treatment by keeping the largest amount of medicine in the bloodstream in the early morning hours (Cutolo, 2012; Hadiet al, 2016).In this instance, drug targeting in the colon or deliberately delayed absorption may be preferred for a consistent therapeutic impact(Buttgereit et al., 2011; Najmuddin et al., 2010; Hadiet al, 2016).Because the drug's release comes after a lag time, it can be supplied in greater quantities when it is most needed.As a result, the disease's peak pain and stiffness symptoms can be overcome and patient compliance can be improved(Najmuddin et al., 2010; Hadiet al, 2016).

Ulcerative colitis(UC) andCrohn's disease(CD) are chronic inflammatory disorders of the terminal part intestine (Nagarjun et al; 2017). In these cases, making the drug available at the site inflammation is one of the strategiesused in their treatments. Hence, it was hypothesized that colon targeted extended-release prednisolone tablets may help to treat inflammatory conditions like RA, UC and CD. Based on the above facts the present study was planned to synthesize and evaluate colon targeted extended-release matrix tablets of prednisolone using pectin and/or xanthan gum as the matrix for extended-release dosage forms.

Material and Methods

Chemicals

Prednisolone was received as a gift sample from Mepro Pharmaceuticals Pvt. Ltd., Mumbai, India.pectin, xanthan gum, microcrystalline cellulose (MCC), talc, magnesium stearate were obtained from SD Fine Chem, Mumbai, India, Eudragit RS100 was obtained as gift samples from Evonik Laboratory, Mumbai, India. All other chemicals and reagents used in the study were of analytical grade.

Drug Polymer Compatibility Studies

Fourier transform infrared(FTIR) analysis
The pure prednisoloneand physical mixture of formulation (F13) withor without prednisolone were crushed with KBr and pellets were made under hydraulic pressure of 600 kg. The FTIR spectra were recordedusing an FTIR spectrophotometer (Make and model of IR) in the range of 4000-400 cm^{-1}at ambient temperature(Dangiet al., 2013; Hadiet al, 2016).

Differential scanning calorimetric (DSC)analysis
The pure prednisoloneand its physical mixture with the selected polymers under studywere heated from 0-300°C at a heating rate of 10° C/min under ARGON atmosphere using a micrometre (DSC Q20 V24.4 Build 116, TA Instruments, USA) and then thermograms were obtained(Dangiet al., 2013; Hadiet al, 2016).

Formulation of Tablets

Prednisolone tablets were prepared by the wet granulation method as per ingredients mentioned inTable 1. Total 13 formulations (F1-F13) were prepared using pectin and/or xanthan gum as matrix for extended-release. Formulation F1-F3 (Uncoated tablets) contain 40, 50 and 60 mg of xanthan gum, respectively. Formulation F4 and F5 contain 60 mg of xanthan gum and they were coated with 5% w/vand 10% w/vof Eudragit RS100 solution, respectively. Formulation F6-F8 (Uncoated tablets) contain 40, 50 and 60 mg of pectin, respectively. Formulations F9 and F10 contain 60 mg of pectin and they were coated with 5% w/vand 10% w/vof Eudragit RS100 solution, respectively. Formulation F11-F13 contain 30 mg of xanthan gum and 30 mg of pectin, F11 is an uncoated tablet and F12 and F13 were coated with 5% w/vand 10% w/vof Eudragit RS100 solution, respectively.

For granulation the wet mass was prepared and passed through a sieve No. 16 and granules were dried at 50°C for 15 min and then sieved again with mess No. 22. The prepared granules were subjected for evaluation precompression parameters such as bulk density, tapped density, Carr's index, Hausner ratio and angle of repose(Dangiet al., 2013; Hadiet al, 2016). Then the granuleswerelubricated with magnesium stearate and talc and compressed using a single punch tablet machine, equipped with flat-faced punches of 9 mm diameter (Rimek mini press-ii, Karnavati Engineering Ltd.).To reduce the repetition of work, the formulation containing the same ingredients and proportion and only differ in the coating were combined during granulation and tablet punching.

The tablets were further coated with Eudragit RS-100 solution (5% w/v or 10% w/v) prepared in the mixture of isopropyl alcohol:acetone (1:1) by immersion followed by dip-coating technique(Dangiet al., 2013; Hadiet al, 2016). The tablets were evaluated for hardness, thickness, friability, weight variation, uniformity of drug content, *in-vitro* release was studied in simulated gastric fluid (pH 1.2, for 2 h) simulated intestinal fluid (pH 7.4, 2-5 h) followed by rat caecal medium (pH 6.8, up to 24 h) as per previously published protocol (Dangi et al., 2013; Mohd et al, 2014; Hadi et al, 2016). Further,the formulation which showed optimum results in the above-studied parameter was evaluated for Roentgenographic study in the rabbit.

In vivo Roentgenographic study of prednisolone tablets

Healthy Rabbit weighing between 4 to 5 kg was used for the study. The optimized formulation F13 was prepared with radio-opaque material barium sulphate to scan the position of the tablet in the GIT. The rabbit was fasted for 12 h before the study and was allowed to have water *ad libitum*. The test formulation was administered orally using oral feeding tube. At an interval of 1, 3, 5, 7, 9, 11 and15 hours, the X-ray photographs were taken to observe shape, integrity, and position of the tablet in the GIT.

Result and Discussion

FTIR Analysis

When the drug-polymer interaction was investigated using FT-IR, there was no evidence of a drug-excipient interaction.The following results were derived from the FTIR spectral interpretation.The FTIR spectrum of prednisolone shows the intense band at 3452.58 cm^{-1} (OH group), 3358.07 $cm^{-1}$and 3043.67 cm^{-1} (aromatic ring), 1653 cm^{-1} (C = O group), 1604.77 cm^{-1} (aromatic C = C bending), 1442.75 $cm^{-1}$and 1386.82 cm^{-1} (CH bending).The peak observed in FTIR of physical mixture of the formulation was found to be at 3452.58 cm^{-1}, 3356.14 cm^{-1}3045.60 cm^{-1}, 1654.92 cm^{-1}, 1604.77 cm^{-1},1448.54 cm^{-1}and1396.46 cm^{-1}, there is no significant shift in the frequencies of the above-mentioned functional groups of prednisolone, indicating that there is no chemical interaction between prednisolone and the physical mixture of the formulation.The spectrum of the prednisolone, physical mixture of formulation (F13)with or without prednisolone, is shown in Figure 1.

DSCanalysis

The thermogram of pure drug exhibited a sharp endothermic peak at 246.91˚ C corresponding to its melting point. The absence of a well-defined chemical interaction between the drug and the formulation mixture was demonstrated by the DSC thermogram of the physical mixture of formulation, which revealed identical peaks corresponding to pure drug.The DSC thermogram of the prednisolone, physical mixture of formulation (F13) with or without prednisolone is shown in Figure 2.

Pre-compression parameters

Pre-compression micrometricproperties of all granules such as bulk density, tapped density, Carr's index, Hausner ratio and angle of repose are represented in Table 2. The bulk density was found in a range of 0.450-0.493, tapped density was in the range of 0.518-0.612, Carr's index was in the range of 14.49-20.36, Hausner ratio was in the range of 1.17-1.22 and angle of repose were in the range of 16°32'-20°26'.The small angle of repose, Carr's index and Hausner's ratio indicated good micrometric behaviour of the granules.The micro-characteristics of all formulations were compared and F13 was found to fit optimally within the specified limits (Dangi et al. 2013).

Tablet Evaluation Parameter

The post tablet compression evaluation parameters results such as hardness, thickness, friability, weight variation, uniformity of drug contentare represented in Table 3.The hardness, thickness, friability, weight variation and uniformity of drug contentin different formulations were found to be almost uniform. The formulation F13 was found to be optimum among the thirteen evaluated tablet formulations. In the case of F13, the thickness was 3 ± 0.03 mm, weight variation was 1.2 ± 0.3, hardness was 5.0 ± 0.2 Kg/cm^2, friability was 0.61 ± 0.2% and drug content was found to be 99.09 ± 1.23%.

In vitro drug release studies

In vitro drug release studies were performed for matrix tablets in simulated gastric fluid (SGF), simulated intestinal fluid (SIF) and simulated caecal fluid (SCF). The first 2 h drug release was studied in SGF (pH 1.2), this acidic environment is used to study the drug release pattern in the stomach environment. In SGF, at the end of 1 h small quantity of drug release was observed from the tablet F1(12.76± 2.4%), F2 (8.67± 2.3%), F3 (2.3± 1.4%), F6 (13.41± 2.1%), F7 (9.80±2.3%) and F8 (1.75 ± 1.2%). In other formulations F4, F5, F9, F10, F11, F12 and F13 no drug release wasobserved at the end of 1st h. All the formulation showing drug release in the first h were uncoated tablets and contain 40 mg, 50 mg and 60 mg of pectin (F1, F2 and F3) or xanthan gum (F6, F7 and F8). The amount of drug release was decreasing with the increased concentration of pectin or xanthan gum in the formulation.

The small quantity of drug release was observed fromformulation F4 (0.20 ± 0.6%) and F9 (0.22 ± 0.6%) at the end of 3 h. Formulation F4 and F9 contained 60 mg of pectin and60 mg of xanthan gum, respectively and they were coated with a 5% solution of Eudragit RS100. The formulations F5 and F10 contain 60 mg of pectin and60 mg of xanthan gum, respectively and they were coated with 5% solution of Eudragit RS100. The drug release in these formulations (F5 and F10) was observed at the end of 4 h. These results indicate that both concentration of matrix (pectin and xanthan gum) and concentration of coating solution are responsible for delaying the drug release from the formulation.

Formulation F11 was prepared using the mixture of pectin and xanthan gum in equal proportion (30 mg each). Interestingly, in this formulation, a small amount

of drug release (0.22 ± 0.6%)was observed at the end of 2 h but not at the end of 1 h. This indicates that the combination of two matrix was beneficial to post pond the initiation of drug release from the matrix tablets. Coating of the formulations containing a combination of pectin and xanthan gum (30 mg each) with 5% (F12) and 10% (F13) solution of Eudragit RS100 further postponed the drug release upto 4 and 5 h respectively. In the case of F12 (0.15 ± 0.4) and F13 (0.14 ± 0.5),a small quantity of drug release was observed at the end of 4 and 5 h, respectively. Formulation F1, F2, F6 and F7 released more than 99% of drug content at the six-hour dissolution study. These formulations were uncoated and prepared using less amount pectin or xanthan gum. The formulation F3 and F8 were also uncoated and contain 60 mg of pectin and xanthan gum, respectively and these tablets released more than 99% of drug at the end of 9 h.

Formulation F4 and F9 were coated with 5% w/v Eudragit RS100 solutionand contain 60 mg of pectin and xanthan gum, respectively they released the drug upto the end of 12 h. The formulation F5 and F10 were coated with 10% w/v Eudragit RS100 solution and contain 60 mg of pectin and xanthan gum, respectively they released the drug upto the end of 13 h. this effect maybe because of the concentration of coating solution.

Formulation F11 was an uncoated tablet contains the mixture of 30 mg of pectin and 30 mg of xanthan gum took 11 h to release 99% of drug from the matrix. The same formulation coated with 5% w/v and 10% w/v of Eudragit RS100 solution in F12 and F13, respectively they took 14 h and 15 h to release 99% of drug content from the matrix. Among the studied formulations, F13 showed optimum results as extended-release colon targeted drug delivery. F13 started drug release at the end of 5 h (0.14 ± 0.5%), more than half of drug was released at the end of 12 h (56.17 ± 2.1%) and continued the drug release upto the end of 15 h (99.54 ± 1.6%). The cumulative percentage drug release study result matrix tablet in SGF, SIF and SCF are shown in Figure 3.

In vivo Roentgenographic study of tablets

The Roentgenographic study showed that the tablet remained intact in the stomach and small intestine. The X-ray photographs were taken at 2 h and 4 h of post-administration showed intactof tablet thereafter slowly intactness was reduced and appeared in colon as in swollen state at 12 h interval. The complete disappearance of the tablet was seen at 24 h intervals that indicate degradation of the tablet. *In vivo* Roentgenographic study photographs are shown in Figure 4.

Conclusion

The prepared tablets met the compendia limits in termsof physiochemical parameters and dissolution studies. The mixture of 30 mg pectin and 30 mg of xanthan gum as matrix and 10% w/v of Eudragit RS100 solution as coating material werebest suitable in colon targeteddrug delivery system to provide optimum prednisolone release and protect it from SGF andSIF. As a result, colon delivery of prednisolone appeared to be apromising alternative to its traditional oral formulation.

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Table 1: Formulation Table

Ingredients(mg/tablet)	Formulation codes												
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Prednisolone	20	20	20	20	20	20	20	20	20	20	20	20	20
Pectin	-	-	-	--	--	40	50	60	60	60	30	30	30
Xanthan gum	40	50	60	60	60	--	--	--	--	--	30	30	30
Microcrystalline cellulose	37	27	17	17	17	37	27	17	17	17	17	17	17
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1	1
Eudragit RS100 solution, Coating (5% w/v)	--	--	--	Yes	--	--	--	--	Yes	--	--	Yes	--
Eudragit RS100 solution, Coating (10% w/v)	--	--	--	--	Yes	--	--	--		Yes	--	--	Yes

Table 2: Precompression Parameters

Formulations	Bulk Density	Tapped Density	Carr's Index (%)	Hausner Ratio	Angle of Repose
F1	0.493	0.612	20.36	1.22	20°26'
F2	0.489	0.577	20.12	1.22	19°55'
F3	0.487	0.567	18.91	1.21	18°70'
F6	0.477	0.549	18.64	1.21	18°32'
F7	0.478	0.552	17.57	1.20	17°86'
F8	0.461	0.535	16.37	1.20	17°64'
F11	0.450	0.518	14.49	1.17	16°32'

Table 3: Evaluation of prednisolone matrix tablets

Formulation	Thickness (mm) n = 6	Weight variation (%) n = 20	Hardness (Kg/cm^2) n = 6	Friability (%) n = 20	Drug Content (%) n = 3
F1	3 ± 0.03	1.5 ± 0.1	4.5 ± 0.1	0.90 ± 0.4	98.95 ± 1.41
F2	3 ± 0.04	1.5 ± 0.3	4.5 ± 0.3	0.84 ± 0.3	99.02± 1.60
F3	3 ± 0.03	1.4 ± 0.2	5.0 ± 0.2	0.66 ± 0.2	98.81 ± 1.43
F4	3 ± 0.06	1.5 ± 0.4	5.0 ± 0.2	0.65 ± 0.3	98.99 ± 1.03
F5	3 ± 0.04	1.5 ± 0.3	5.0 ± 0.3	0.64 ± 0.3	99.12 ± 1.33
F6	3 ± 0.05	1.3 ± 0.2	4.5 ± 0.2	0.95 ± 0.3	98.85 ± 1.56
F7	3 ± 0.03	1.6 ± 0.3	4.5 ± 0.1	0.86 ± 0.2	98.89 ± 1.23
F8	3 ± 0.06	1.5 ± 0.3	5.0 ± 0.2	0.67 ± 0.4	99.15 ± 1.37
F9	3 ± 0.04	1.6 ± 0.2	5.0 ± 0.3	0.63 ± 0.3	98.83 ± 1.64
F10	3 ± 0.05	1.8 ± 0.4	5.0 ± 0.2	0.62 ± 0.2	98.99 ± 0.95
F11	3 ± 0.03	1.4 ± 0.2	5.0 ± 0.3	0.63 ± 0.3	99.43 ± 1.28
F12	3 ± 0.04	1.2 ± 0.4	5.0 ± 0.1	0.62 ± 0.3	99.14 ± 1.20
F13	3 ± 0.03	1.2 ± 0.3	5.0 ± 0.2	0.61 ± 0.2	99.09 ± 1.23

The values are expressed in mean ± S.D.

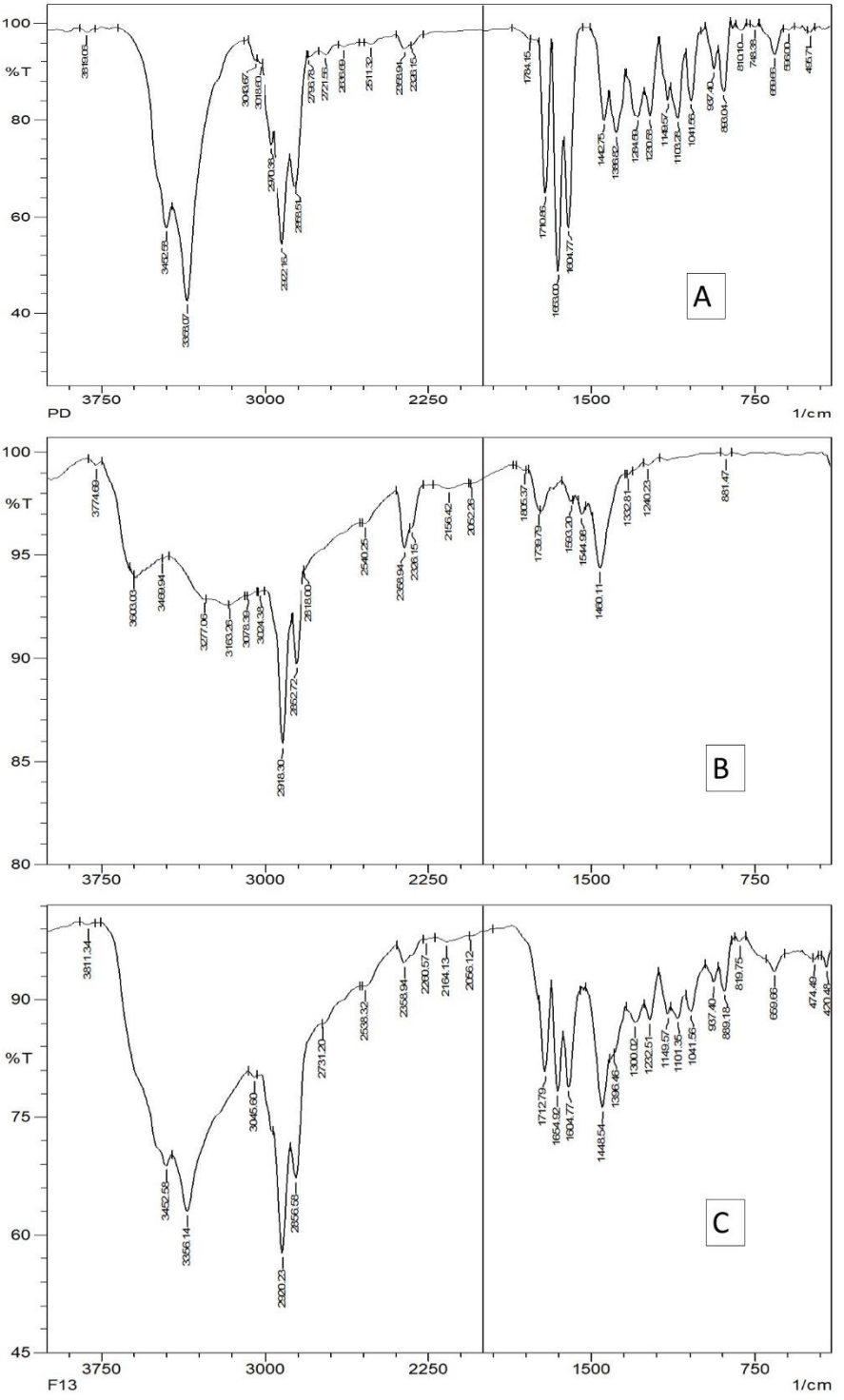

Figure 1: FT-IR graph ofA] Prednisolone, B] Dummy formulation and C] Physical mixture of formulation (F13)

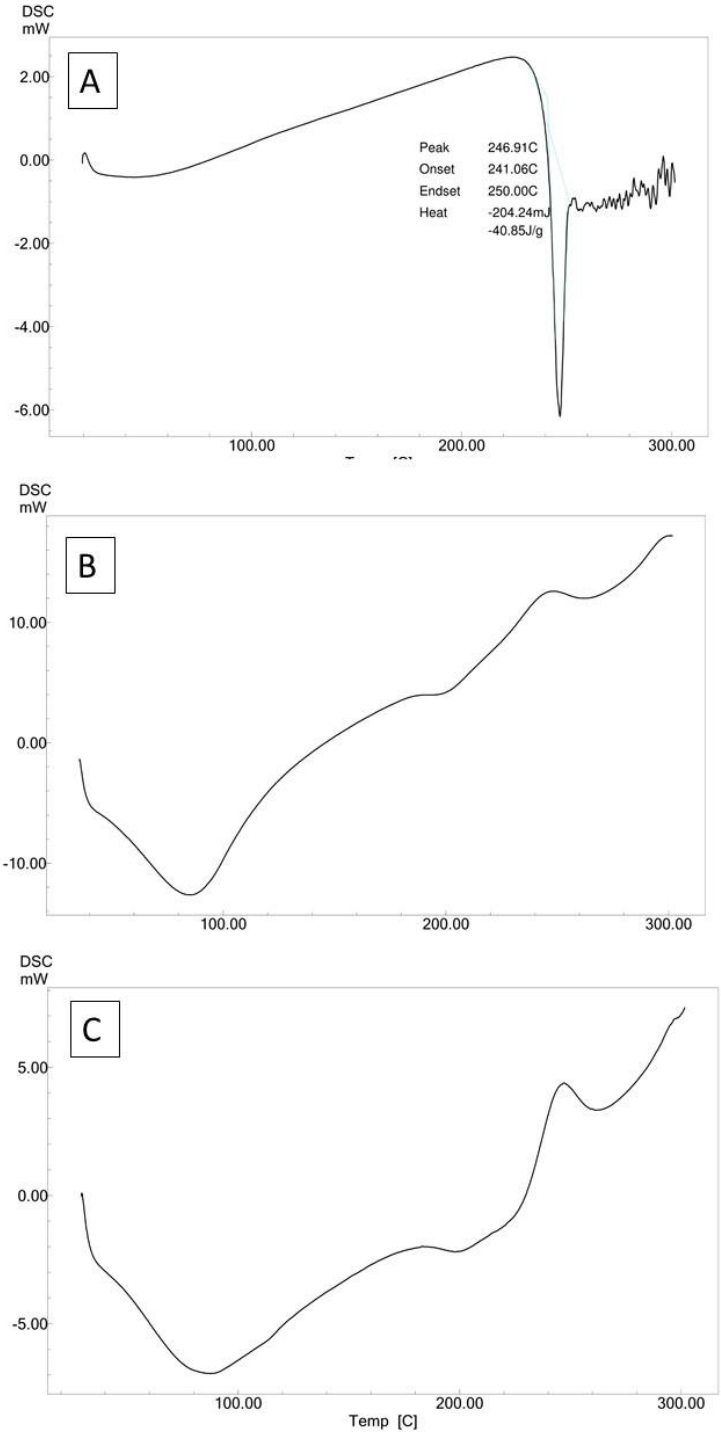

Figure 2: DSC thermogram of A] Prednisolone, B]Dummy formulation and C] Physical mixture of formulation (F13)

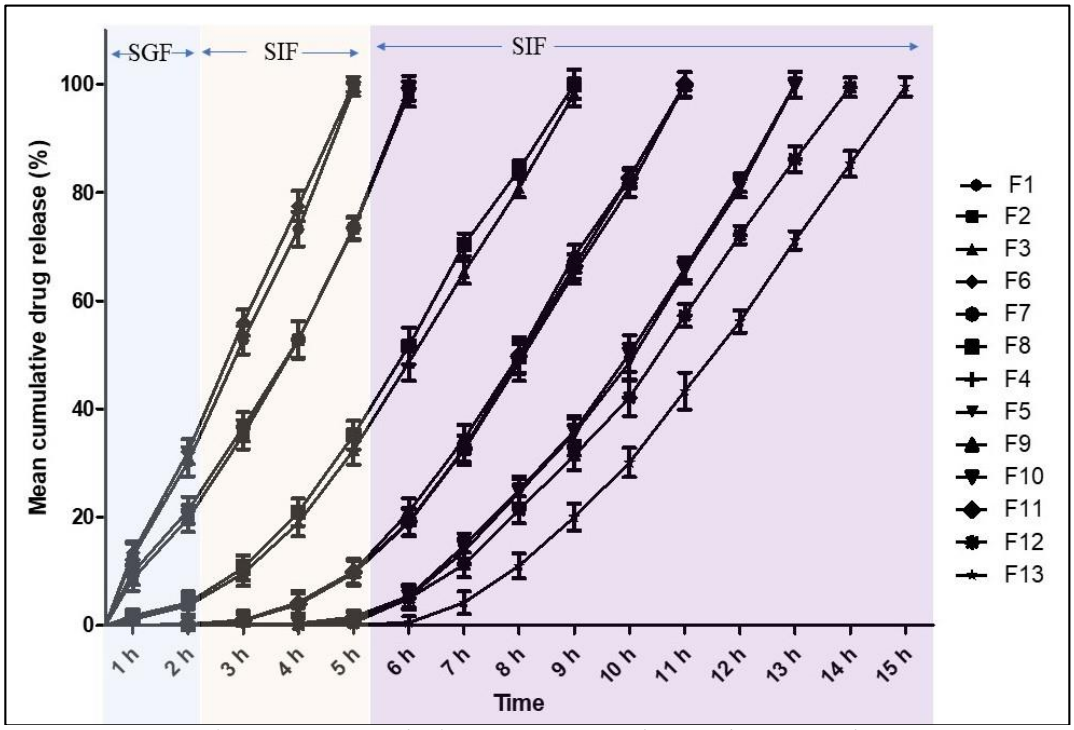

Figure 3: Cumulative percentage drug release study

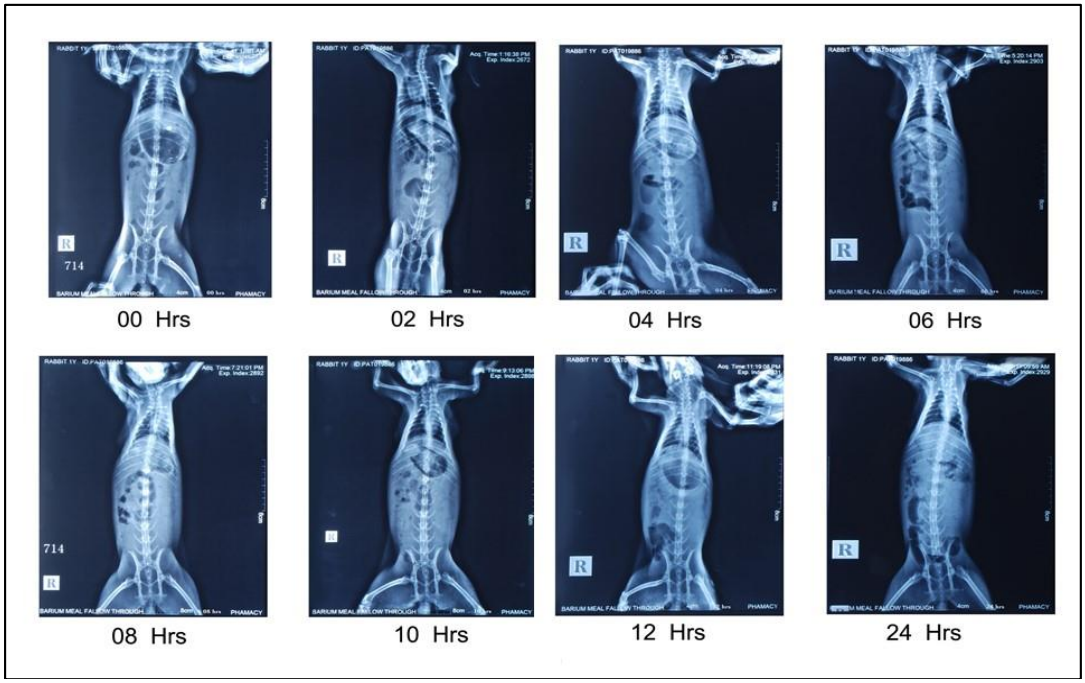

Figure 4: In vivo Roentgenographic study photographs