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RESEARCH ARTICLE OPEN ACCESS

PREPARATION AND EVALUATION OF CONTROLLED RELEASE TABLETS CONTAINING IBUPROFEN

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ABSTRACT

Introdução: The article discusses the general provisions of the feasibility study for the use of dual completion operation on the example of the experience of Turkmenistan, where an experimental test was conducted on four wells of the Northern Goturdepe field located in the coastal zones of the coastal waters of the Caspian Sea. Geological materials and materials of previously drilled wells were used for the design, as well as analysis of hydrodiamic and thermodynamic indicators from the existing well stock. Oil samples were also taken from wells in order to conduct laboratory analyses to fully determine their characteristics. The calculation of the economic efficiency of these four wells was carried out, according to the results of which the economic effect was determined by reducing capital expenditures for drilling and development of a multi-layer field. This work can be used and useful to fulfill the tasks set for the accelerated development of multi-layer deposits, which will eventually lead to a significant reduction in the volume of drilling wells, respectively, and funds.

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INTRODUCTION

Controlled release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or uniform blood levelof a drug often translates into better patient compliance, as well as enhanced clinical efficacyof the drug for its intended use. The first Controlled release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida. Controlled release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. The goal in designing Controlled or Controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, Controlled release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ.

Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulations:

- If the active compound has a long half-life, it is Controlled on its own,
- If the pharmacological activity of the active is not directly related to its blood levels,
- If the absorption of the drug involves an active transport and
- If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.

The above factors need serious review prior to design. Introduction of matrix tablet as Controlled release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is

widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of Controlled release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of Controlled release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the Controlled release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane-controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water-soluble drugs.

Rationale for Extended-Release Dosage Forms[10-12]: Some drugs are inherently long lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up doses, and noncompliance with the regimen. When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose. However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of sub therapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient. Extended-release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended-release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period. The Controlled plasma drug levels provided by extended-release products oftentimes eliminate the need for night dosing, which benefits not only the patient but the caregiver as well.

Drawbacks of Conventional Dosage Forms[13]:

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
3. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

MATERIALS

Ibuprofen Provided by SURA LABS, Dilsukhnagar, Hyderabad, HPMC K 15M, Yarrow chemicals (Mumbai,India), HEC 2MSd fine chemicals Bombay, India, HPC 2M Arvind Remedies Ltd, Tamilnadu, India, Magnesium Stearate Merck Specialities Pvt Ltd.

METHODOLOGY

Characterization of Ibuprofen

Organoleptic properties: Take a small quantity of sample and spread it on the white paper and examine it visually for color, odour and texture.

Determination of IbuprofenMelting point : The melting point of Ibuprofen was determined by capillary tube method according to the USP. A sufficient quantity of Ibuprofen powderwas introduced into the capillary tube to give a compact column of 4-6mm in height. The tube was introduced in electrical melting pointapparatus and the temperature was raised. The melting point wasrecorded, which is the temperature at which the last solid particle ofIbuprofen in the tube passed into liquid phase**.**

Determination of Ibuprofen Solubility: Determination of solubility of drug by visual observation. Anexcess quantity of Ibuprofen was taken separately and adds in10 ml of different solutions. These solutions were shaken wellfor few minutes. Then the solubility was observed andobservations are shown in the Table.

Analytical method development

Determination of Wavelength: 10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

Determination of Calibration Curve: 10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table 8.1 and 8.2) and those concentrations absorbance were found out at required wavelength.

Preformulation parameters: The quality of tablet, once formulated by rule, is generally dictated by thequality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Table 1. Formulation composition for tablets

Formulation code	API	Polymers			Diluent	Glidant	Lubricant	Total weight
	Ibuprofen	HPMC K 15M	HEC 2M	HPC 2M	MCC	Aerosil	Magnesium Stearate	
F1	100	50	-	-	235	7	8	400
F2	100	100	-	-	185	7	8	400
F3	100	150	-	-	135	7	8	400
F4	100	-	50	-	235	7	8	400
F5	100	-	100	-	185	7	8	400
F6	100	-	150	-	135	7	8	400
F7	100	-	-	50	235	7	8	400
F8	100	-	-	100	185	7	8	400
F9	100	-	-	150	135	7	8	400
All the quantities were in mg								

Angle of repose: The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force.

RESULTS AND DISCUSSION

The present study was aimed to develop controlled release tablets of Ibuprofen using various polymers. All the formulations were evaluated for physicochemical properties and in vitro drug release studies.

Analytical Method: Graphs of Ibuprofen were taken in 0.1N HCL and in pH 6.8 phosphate buffer at 262 nm and 266nm respectively.

Table 2. Observations for graph of Ibuprofen in 0.1N HCL

Concentration (µg/ml)	Absorbance
0	0
2	0.176
4	0.314
6	0.452
8	0.593
10	0.738

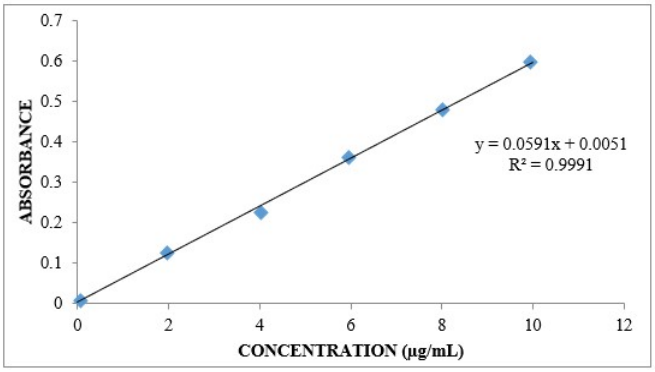

Fig. 1. Standard curve of IBUPROFEN

Table 3. Standard graph values ofIbuprofenat 266nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
2	0.132
4	0.234
6	0.364
8	0.482
10	0.591

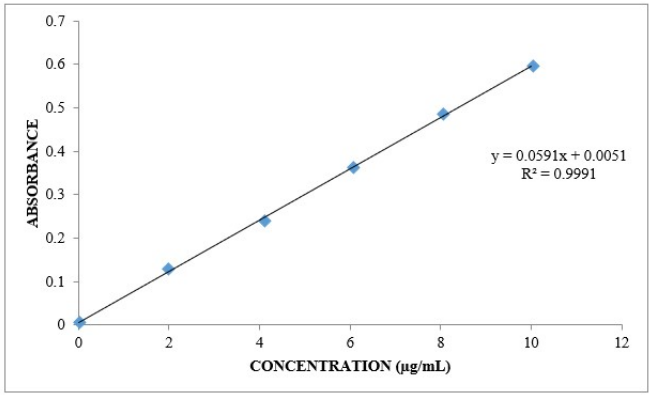

Fig. 2. Standard curve of Ibuprofen

Preformulation parameters of powder blend

Table 4. Pre-formulation parameters of Core blend

Formulation code	Angle of repose (Θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	28.46	0.5710	0.6897	17.21	1.121
F2	28.48	0.5698	0.6701	14.96	1.176
F3	28.46	0.5725	0.6909	17.14	1.206
F4	28.40	0.5702	0.6782	15.92	1.189
F5	28.71	0.5620	0.6787	17.99	1.207
F6	28.70	0.5602	0.6698	17.11	1.196
F7	28.65	0.5562	0.6714	16.36	1.207
F8	28.80	0.5665	0.6813	16.85	1.203
F9	28.02	0.5581	0.6775	17.62	1.214

All the values represent n=3

Table 5. *In vitro* quality control parameters for tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thick ness (mm)	Drug content (%)
F1	398.15	5.6	0.26	4.92	96.18
F2	400.25	5.3	0.32	4.69	99.82
F3	399.39	5.0	0.46	4.87	97.60
F4	397.52	4.9	0.51	4.35	99.72
F5	400.10	5.2	0.63	4.16	100.05
F6	396.57	4.8	0.72	4.61	98.76
F7	398.61	5.5	0.39	4.38	97.61
F8	399.72	5.7	0.46	4.76	98.27
F9	397.95	5.3	0.62	4.37	99.34

***In Vitro* Drug Release Studies**

Table 6. Dissolution Data of Ibuprofen Tablets

TIME (H)	CUMULATIVE % OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
In dissolution media 0.1 N HCL									
0	0	0	0	0	0	0	0	0	0
0.5	20.89	18.53	15.42	31.28	21.05	16.59	19.61	15.72	13.17
1	28.19	26.10	20.91	40.17	29.79	23.12	25.07	20.91	18.93
2	39.05	34.68	26.25	45.31	36.04	32.53	36.20	26.42	23.55
In dissolution media 6.8 Phosphate Buffer									
3	49.71	43.03	38.85	53.58	43.10	40.28	45.16	30.64	28.47
4	61.14	50.96	42.96	66.76	47.65	45.10	52.92	36.80	32.24
5	68.89	61.24	57.69	72.18	54.96	50.37	59.33	41.16	40.89
6	76.63	69.73	61.52	82.44	63.25	57.05	66.96	49.77	47.51
7	83.56	76.19	76.07	90.16	78.79	62.83	70.05	54.23	51.46
8	96.12	82.88	80.61	98.90	87.91	68.95	75.60	62.15	60.89
9	98.37	87.67	86.40		92.01	74.32	79.81	67.73	65.95
10		92.78	91.31		97.84	88.08	83.37	71.81	67.11
11		97.23	94.57			98.10	93.02	87.22	72.25
12			99.08				95.38	90.64	87.37

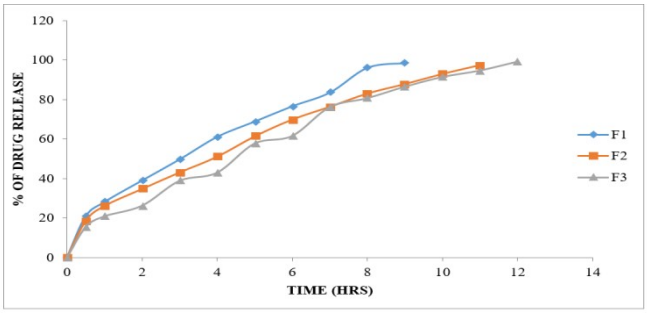

Fig. 3.Dissolution profile of Ibuprofen (F1, F2, F3 formulations)

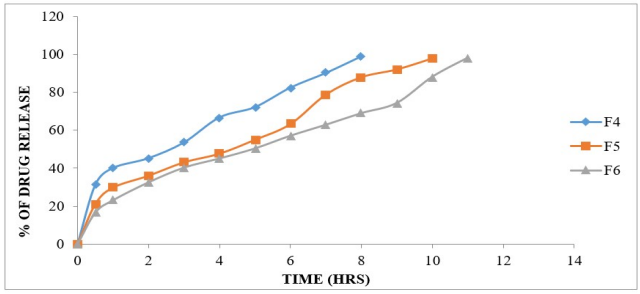

Fig. 4. Dissolution profile of Ibuprofen (F4, F5, F6 formulations)

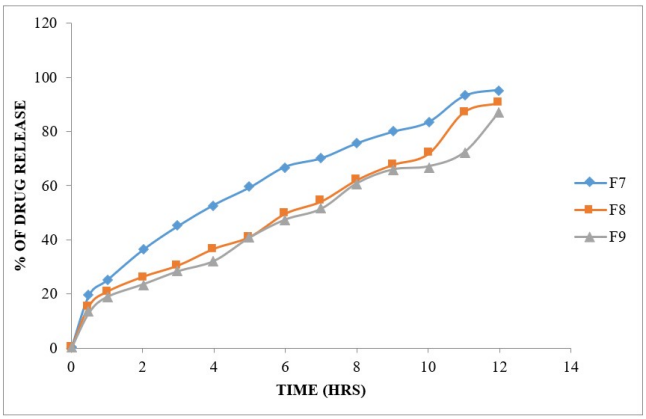

Fig. 5. Dissolution profile of Ibuprofen (F7, F8, F9 formulations)

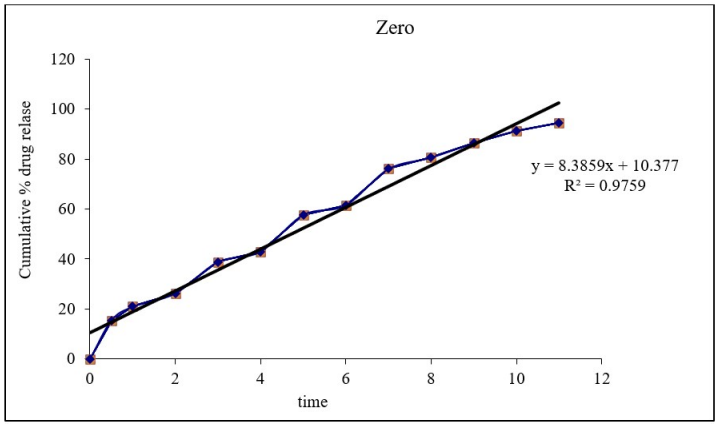

Fig. 6. Zero order release kinetics graph

Table 7. Release Kinetics

Cumulative (%) release q	Time (t)	root (t)	Log(%) release	log (t)	log (%) remain	release rate (cumulative % release / t)	1/cum% release	Peppas log q/100	% drug remaining	Q01/3	Qt1/3	Q01/3-qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
15.42	0.5	0.707	1.188	-0.301	1.927	30.840	0.0649	-0.812	84.58	4.642	4.390	0.252
20.91	1	1.000	1.320	0.000	1.898	20.910	0.0478	-0.680	79.09	4.642	4.292	0.349
26.25	2	1.414	1.419	0.301	1.868	13.125	0.0381	-0.581	73.75	4.642	4.194	0.448
38.85	3	1.732	1.589	0.477	1.786	12.950	0.0257	-0.411	61.15	4.642	3.940	0.702
42.96	4	2.000	1.633	0.602	1.756	10.740	0.0233	-0.367	57.04	4.642	3.849	0.792
57.69	5	2.236	1.761	0.699	1.626	11.538	0.0173	-0.239	42.31	4.642	3.485	1.157
61.52	6	2.449	1.789	0.778	1.585	10.253	0.0163	-0.211	38.48	4.642	3.376	1.266
76.07	7	2.646	1.881	0.845	1.379	10.867	0.0131	-0.119	23.93	4.642	2.882	1.760
80.61	8	2.828	1.906	0.903	1.288	10.076	0.0124	-0.094	19.39	4.642	2.687	1.955
86.4	9	3.000	1.937	0.954	1.134	9.600	0.0116	-0.063	13.6	4.642	2.387	2.255
91.31	10	3.162	1.961	1.000	0.939	9.131	0.0110	-0.039	8.69	4.642	2.056	2.586
94.57	11	3.317	1.976	1.041	0.735	8.597	0.0106	-0.024	5.43	4.642	1.758	2.884
99.08	12	3.464	1.996	1.079	-0.036	8.257	0.0101	-0.004	0.92	4.642	0.973	3.669

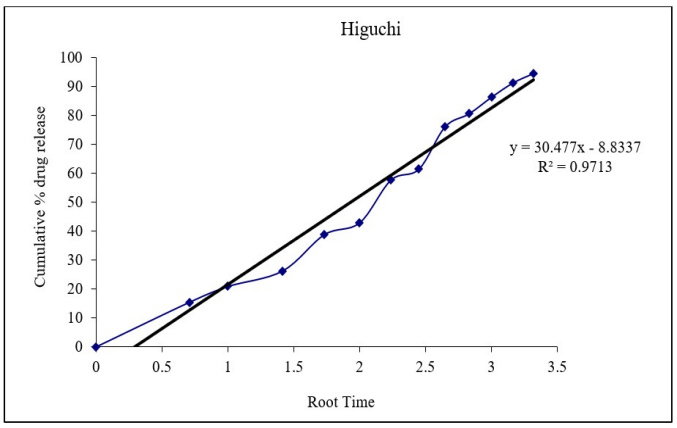

Fig. 7. Higuchi release kinetics graph

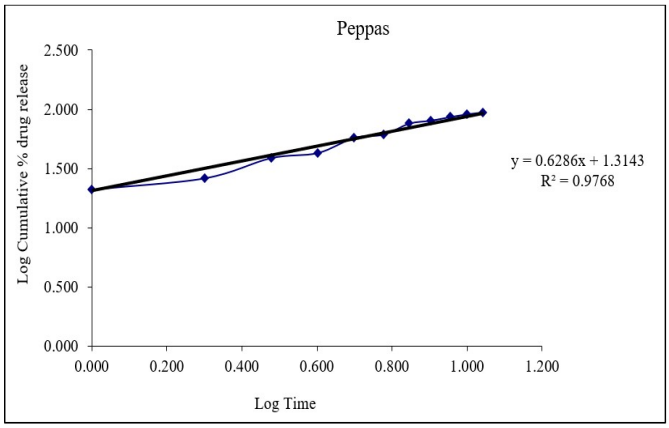

Fig. 8. Peppas release kinetics graph

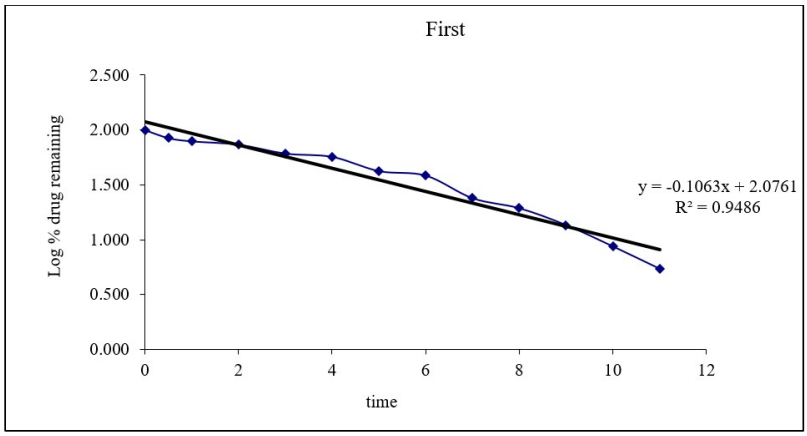

Fig. 9. First order release kinetics graph

Drug – Excipient compatibility studies

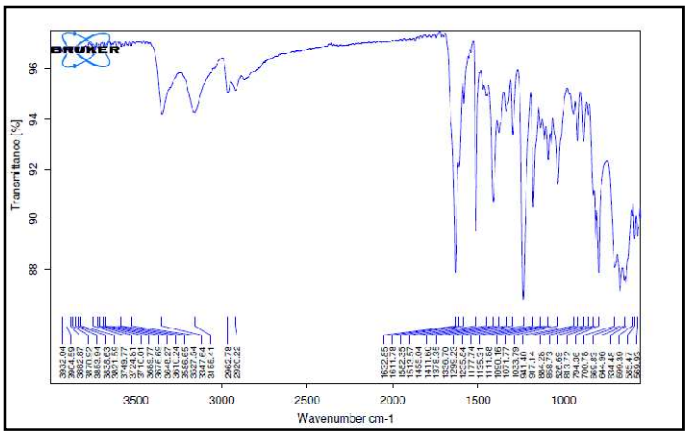

Fig. 10. FT-TR Spectrum of Ibuprofen pure drug

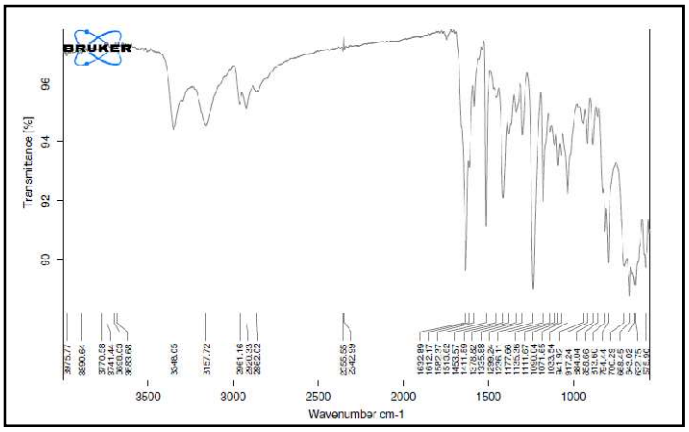

Fig. 11. FT-IR Spectrum of Optimised Formulation

CONCLUSION

Morphological characteristics such as colour, odour, form etc; of Ibuprofen were studied. As the API is found to be white colour and odourless. The Melting point of Ibuprofen lies in the range between 75-77.5 ˚C, whichindicates the purity of the drug. The solubility of Ibuprofen was analysed in various solvents. Flow properties of API were studied by performing tests like Angle of repose,bulk density, tapped density, Carr's index, Hausner's ratio. The results indicate thatAngle of repose indicating goodflow properties. The Carr's index was found to be 17.62% indicating fair to passable. The Hausner's ratio waswithin the limits indicating free flowability. These results indicated the drugpossessed good flow properties and compressible characteristics. IR spectra of physical mixture of drug and excipients, drug alone showed nosignificant shift or reduction in intensity of peaks of Ibuprofen. The studies showedthat there was no interaction or physical change between the drug and excipients. Sothe selected excipients were found to be compatible with the drug.

Estimation of Ibuprofen was performed by UV spectrophotometric method. Themethod obeyed Beer's of drug and law in the concentration range of 0-10µg/ml. Thusthe method was found to be suitable for estimation of Ibuprofen content in variousproducts and *in vitro* dissolution studies. Ibuprofen along with other excipients was formulated into tablets by direct compression methods as per the formulae given in the table no7.3. HPMC K 15M, HEC 2M and HPC 2M polymers was used ingraded amounts as to control the rate of release. Tablet quality control tests such as weight variation, hardness, friability, thickness and drug release studies in different media were performed on the compression tablet and found within the limits. Among all the tablets formulated, formulation F3 prepared by direct compression method gave the highest dissolution(99.08%) in a controlled release manner.So formulation F3 was considered as best and optimized for the preparation of tablets of Ibuprofen prepared by direct compression methods.

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